Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Alimera Sciences Limited

MHRA Inspection Number: Insp GPvP 41472/11479781-0003

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAPA	Corrective and Preventative Action
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organisation
DMO	Diabetic Macular Oedema
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GVP	Good Vigilance Practice
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit Risk Evaluation Report
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk Management Plan
SAE	Serious Adverse Event
SDEA	Safety Data Exchange Agreement
SOP	Standard Operating Procedure
UK	United Kingdom

SECTION A: INSPECTION REPORT SUMMARY

Inspection type:	Statutory National Inspection
System(s) inspected:	Alimera Sciences Limited At the time of the inspection no UKPSMF number had been assigned yet.
Site(s) of inspection:	Alimera: Remote inspection [redacted] study investigator site (site [redacted] : [redacted]
Main site contact:	[redacted] EU QPPV/UK QPPV PrimeVigilance s.r.o. Stetkova 18 140 00 Praha 4 The Czech Republic Mobile: [redacted] E-mail: [redacted] [redacted] Associate Director, Drug Safety Alimera Sciences Limited Royal Pavilion, Wellesley Road Aldershot GU11 1PZ United Kingdom Mobile: [redacted] E-mail: [redacted]
Date(s) of inspection:	Alimera: 20-24 September and 13-14 October 2021 [redacted] study investigator site (site [redacted] 28 June–01 July 2022, 12 July 2022
Lead Inspector:	[redacted]
Accompanying Inspector(s):	[redacted] (MAH inspection) [redacted] (investigator site inspection)
Previous inspection date(s):	n/a
Purpose of inspection:	Inspection of the pharmacovigilance system to review compliance with UK and EU requirements in relation to non-interventional PASS.
Study selected to provide system examples:	[redacted] An Open Label, Registry Study Of The Safety Of [redacted]
Name and location of UK QPPV:	[redacted] EU QPPV/UK QPPV PrimeVigilance s.r.o. Stetkova 18 140 00 Praha 4

	The Czech Republic Contact details as above.
Global PV database (in use at the time of the inspection):	[redacted]
Key service provider(s):	Pharmacovigilance services provided by PrimeVigilance [redacted] Contract research organisation: Aibili Data management: LINK Medical Writing of the final study report: Jeniss Research
Inspection finding summary:	1 Critical finding 4 Major findings 6 Minor findings
Date of first issue of report to MAH:	21 December 2022
Deadline for submission of responses by MAH:	Initial: 30 January 2023, extension to 28 February 2023 agreed on 05 January 2023 Follow-up 1: 04 August 2023, extended to 29 August 2023 on 28 July 2023
Date(s) of receipt of responses from MAH:	Initial: 28 February 2023 Follow-up 1: 29 August 2023
Date of final version of report:	26 September 2023
Report author:	[redacted] Head of GPvP and Senior Pharmacovigilance Inspector

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Alimera Sciences Limited (hereafter 'Alimera') was selected for routine inspection as part of the MHRA's statutory, national pharmacovigilance inspection programme. The purpose of the inspection was to review compliance with currently applicable UK and EU pharmacovigilance regulations and guidelines relevant to the planning, conduct and reporting of non-interventional post-authorisation safety studies (NI-PASS). In particular, reference was made to The Human Medicines Regulations 2012 as amended, Commission Implementing Regulation (EU) No 520/2012 and the EU good pharmacovigilance practices (GVP) Modules as modified by the guidance note 'Exceptions and modifications to the EU GVP that apply to UK MAHs and the licensing authority'.

A list of reference texts is provided at Appendix I.

Alimera is the marketing authorisation holder (MAH) of [redacted]

Alimera's headquarter is located in Alpharetta, Georgia, USA, with offices also located in the UK, Germany, Portugal and Ireland. Pharmacovigilance activities are outsourced to PrimeVigilance, including the UK QPPV role and key pharmacovigilance activities such as global ICSR management and reporting, signal management, PSUR and RMP development.

This inspection was conducted to review in detail the conduct and reporting of the RMP category 1 PASS [redacted] which was completed at the time of the inspection. The study was sponsored by Alimera and was imposed as a specific obligation and condition to the marketing authorisation for [redacted] as part of the marketing authorisation approval process.

The study was aimed at assessing the safety in patients treated with [redacted] The specific objectives included the study of:

- Known safety risks
  - [redacted]
- Potential safety risks
  - [redacted]

- Unknown safety risks

- Safety in patients who have received [redacted] in both eyes during the study.
- The change from baseline visual acuity (VA).

The first patient, first visit was on 14 April 2014. Last patient, last visit was on 09 January 2020 and the final study report [redacted] was submitted to MHRA on 22 December 2020. In total, 562 patients were enrolled of which 393 completed the study. Investigator sites in the UK, Germany and Portugal participated in the study.

Please refer to section C.1 for a summary of significant changes to the study protocol and conduct during the study duration.

Study management activities, including project set-up and management, study submissions, site initiation and close-out visits, and EDC and data management were subcontracted to Aibili for all territories; however, discrete tasks were further subcontracted to other vendors:

- [redacted] development of the [redacted] eCRF.
- [redacted] eCRF development, data management and validation activities, clean file procedures.
- [redacted] UK regulatory submissions and site initiation and close-out visits.

Statistical analysis of the study data for the final study report was subcontracted to an individual statistician and medical writing of the final study report was subcontracted to Jeniss Research.

The investigator site selected for inspection was site [redacted] which had participated in the study since 01 July 2015 and had 21 enrolled patients. 18 patients completed the study, while three patients withdrew due to death or adverse events. The investigator site inspection was conducted to examine how Alimera coordinated and managed this NI-PASS at a site level.

B.2 Scope of the inspection

The inspection focussed on a review of systems and processes that were associated with non-interventional PASS.

The inspection of Alimera was performed remotely 20 – 24 September and 13 – 14 October 2021 using interviews and document review. Personnel involved in pharmacovigilance and study management activities were available via videoconference throughout the inspection for ad-hoc queries.

One investigator site inspection was conducted for study [redacted] on 28 June – 01 July 2022 and 12 July 2022 at investigator site [redacted]

Onsite inspection activities consisted of source document and data review while interviews were conducted remotely via videoconference on day 1 and 2 of the investigator site inspection.

The systems reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plan (attached as Appendix II).

B.3 Documents submitted prior to the inspection

The company submitted a PSMF (version [redacted] effective date [redacted] to assist with inspection planning and preparation. Specific additional documents were also requested by the inspection team and provided by the company prior to the inspection. Details of these requests are contained within document request sheet A and B.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan. The inspection of Alimera was not completed during the allocated inspection days (20 – 24 September 2021) and was continued on 13 – 14 October 2021. In addition, an extra day was required on 12 July 2022 for the investigator site inspection as not all patient files were available during the site visit on 30 June and 01 July 2022.

Closing meetings were held to review the inspection findings on the following dates:

- Alimera MAH inspection: 14 October 2021
- Site [redacted] 12 July 2022

A list of the personnel who attended the closing meeting is contained in the Closing Meeting Attendance Record, which will be archived together with the inspection notes, a list of the documents requested during the inspection and the inspection report.

SECTION C: INSPECTION FINDINGS

C.1 Summary of significant changes and action taken since the last inspection

This was the first MHRA pharmacovigilance inspection of the company. However, during the course of the [redacted] study, the following significant changes were made to the Alimera pharmacovigilance system:

- Changes in the EU QPPV during the duration of the study:
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Changes in functions carrying out ICSR management and reporting activities:
  - Alimera (2014 – April 2017)
  - [redacted] was contracted to carry out ICSR management and reporting activities in 2016, with the first ICSR being processed in April 2017
  - [redacted] is acquired by PrimeVigilance in 2016 and processes are changed to PrimeVigilance procedures on 01 May 2020.
- The global safety database [redacted] was hosted by [redacted] until July 2020, when it was migrated to the [redacted] iteration hosted by PrimeVigilance.

In addition, the following changes were made to the [redacted] study protocol and conduct:

- Protocol amendment [redacted] to allow the retrospective enrolment of patients in the study.
- Protocol amendment [redacted] Change the recruitment goal from 800 to 550 patients. Change in the study duration from five years from the enrolment date of the first prospectively enrolled patient to 6.5 years.
- The eCRF was changed from [redacted] to [redacted] in March 2015.

C.2 Definitions of inspection finding gradings

Critical (CR): a deficiency in pharmacovigilance systems, practices or processes that adversely affects the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation of applicable legislation and guidelines.

Major (MA): a deficiency in pharmacovigilance systems, practices or processes that could potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of applicable legislation and guidelines.

Minor (MI): a deficiency in pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients.

Comment: the observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

The factual matter contained in the Inspection Report relates only to those things that the inspection team saw and heard during the inspection process. The inspection report is not to be taken as implying a satisfactory state of affairs in documentation, premises, equipment, personnel or procedures not examined during the inspection.

Findings from any inspection that covers products authorised in respect of Northern Ireland which are graded as critical or major will be shared with the EMA, EU competent authorities and the European Commission.

C.3 Guidance for responding to inspection findings

Responses to inspection findings should be clear, concise and include proposed actions to address both the identified deficiency and the root cause of the deficiency. Consideration should also be given to identifying and preventing other potential similar deficiencies within the pharmacovigilance system.

Responses should be entered directly into the table(s) in section C.4. The following text is intended as guidance when considering the information that should be entered into each of the fields within the table(s). 'Not applicable' should be entered into the relevant field if the requested information is not appropriate for the finding in question.

Root Cause Analysis Identify the root cause(s) which, if adequately addressed, will prevent recurrence of the deficiency. There may be more than one root cause for any given deficiency.
Further Assessment Assess the extent to which the deficiency exists within the pharmacovigilance system and what impact it may have for all products. Where applicable, describe what further assessment has been performed or may be required to fully evaluate the impact of the deficiency e.g. retrospective analysis of data may be required to fully assess the impact.
Corrective Action(s) Detail the action(s) taken / proposed to correct the identified deficiency.
Preventative Action(s) Detail the action(s) taken / proposed to eliminate the root cause of the deficiency, in order to prevent recurrence. Action(s) to identify and prevent other potential similar deficiencies should also be considered.
Deliverable(s) Detail the specific outputs from the proposed / completed corrective and preventative action(s). For example, updated procedure/work instruction, record of re-training, IT solution.
Due Date(s) Specify the actual / proposed date(s) for completion of each action. Indicate when an action is completed.

Further information relating to inspection responses can be found under 'Inspection outcomes' at: https://www.gov.uk/guidance/good-pharmacovigilance-practice-gpvp

C.4 Inspection findings

C.4.1 Critical findings

CR.1 Conduct of post-authorisation safety studies

Requirements:

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916), Part 11 Pharmacovigilance
Regulation 182(2)
"The holder must (as part of its pharmacovigilance system)--
(c) operate a risk management system for the product in accordance with the risk management plan (if any) for the product (subject to regulation 183);"

Commission Implementing Regulation (EU) No 520/2012
Article 11(d)
"*Specific quality system procedures and processes shall be in place in order to ensure the following: […] the quality, integrity and completeness of the information submitted on the risks of medicinal products […]*"

Article 36
"*The marketing authorisation holder shall ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information […]*"

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)
VI.C.1.2.1.1. Non-interventional post-authorisation studies with a design based on primary data collection
"Information on all adverse events should be collected and recorded from healthcare professionals or consumers in the course of the study unless the protocol provides with a due justification for not collecting certain adverse events"

GVP Module VIII – Post-authorisation safety studies (Rev 3)
VIII.B.7. Quality systems, audits and inspections
"*The marketing authorisation holder shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified.*"

RMS Day 210 Final Assessment Report for [redacted]
I Recommendation
"*[…] the RMS considers that the application for [redacted] …] is approvable provided that the applicant complies with the recommendations for product information and commits to perform a number of specific obligations to be reported back to the RMS and CMS within predefined timeframes.*"

VI Recommended Conditions For Marketing Authorisation And Product Information
"*Specific Obligations:*

Area	*Description*
Pharmacovigilance	*The applicant commits to a 5-year post-authorisation registry study "An open label, registry study of the safety of [redacted] n patients with [redacted] and should submit interim and final reports at 3 years and 5 years*

	respectively, as well as updates within the Periodic Safety Update Report (PSUR) submissions every 6 months. The full study protocol should be submitted within three months of marketing authorisation approval."

The specific study objectives outlined in the [redacted] protocol section 4 *Study Objectives and Purpose* (Amendment [redacted] dated [redacted] were aligned with the known, potential and missing safety risks described in the [redacted] RMP and this included potential systemic events associated with the use of corticosteroids.

In addition, the protocol stated in section 11 with regards to the collection of adverse events that "*All adverse events either observed by the investigator or site staff, or reported by the patient spontaneously, or in response to the direct question below, will be noted in the adverse events section of the patient's CRF and/or in the source document. […] In an attempt to optimize consistency of adverse event reporting, the patient should be asked a standard question to elicit any adverse events. At each clinic or telephone evaluation of the patient, study personnel will ask the following question: "Have you had any problems since your last visit or telephone call?"*"

During the investigator site inspection at site [redacted], significant failures in identifying and reporting systemic adverse events from the hospital records for patients enrolled in the [redacted] study were identified.

At this site, patient health records were split across an ophthalmology-specific patient file and a hospital-wide 'general' patient file. During the inspection of site [redacted] site staff described that they had not reviewed any patient medical records that did not belong to the ophthalmic department to identify any systemic, non-ophthalmic adverse events. Instead, the study team relied on patients to inform them about any non-ophthalmic adverse events at study follow-up visits.

The critical finding related to a lack of oversight by Alimera and a lack of robust processes in place at the time of the [redacted] study to ensure that information was collected by investigator sites to meet all objectives of the study as defined in the approved study protocol. Therefore there was no assurance that complete and accurate information in the final study report had been submitted to competent authorities.

Finding CR.1 a)

Following review of all hospital patient records for four patients [redacted] site [redacted] several adverse events that occurred during the course of the study were identified for three patients, at least four of which met the definition of a serious adverse event in accordance with GVP VI.A.1.6. None of these events had been entered into the EDC. In addition, study-related visits were conducted with the patient after the occurrence of these events where the question on whether any adverse events had occurred since the last visit was marked as 'no' in the source documentation and EDC:

- Patient [redacted] (enrolled on 20 November 2015, treated with [redacted] on 20 November 2015 (left eye) and 11 March 2016 (right eye), end of study visit conducted on 04 April 2019):
  - Record of [redacted] dated 03 September 2017 and a GP letter dated 05 September 2017 described that the patient fell over in her bathroom on 02 September 2017 which resulted in a closed fracture of the humeral head. Study-related follow-up visits took place on 18 September 2017 and 30 November 2017.

- Patient [redacted] (enrolled 12 February 2016, treated with [redacted] on 06 May 2016 (left eye), end of study visit conducted on 10 May 2019):
  - A GP referral to the Cardiology Department dated 07 June 2017 was made due to drop attacks ("*his legs have suddenly given way and he is on the floor with no warning and no pain*") following addition of [redacted] to his prescribed medicines to control hypertension. A study-related follow-up visit took place on 09 November 2017.
  - A referral to the Cardiology department and inpatient discharge summary (both dated 06 April 2018) stated diagnoses of "*Pulmonary oedema and leg oedema*" and "*Congested cardiac failure*". Study-related follow-up visits took place on 03 May 2018 and 20 November 2018.
  - Records of GP visit on 23 January 2019 for a referral to the Neurology department stated "*Increasing unsteadiness with right sided cerebellar signs*".

- Patient [redacted] (enrolled 17 August 2016, treated with [redacted] on 17 August 2016 (left eye), end of study visit conduced on 03 September 2019):
  - Admission to the Accident & Emergency (A&E) department on 16 November 2018 due to a non-ST-elevation myocardial infarction (NSTEMI). A study-related follow-up visit took place shortly after on 05 December 2018.
  - Admission to A&E on 28 December 2018 with the primary presentation of "*right leg wound and cellulitis (previous CABG)*". The patient remained in hospital for several weeks and the medical notes document that there was an infected leg wound from the CABG (Coronary artery bypass graft) in the right leg and low haemoglobin. A study-related follow-up visit took place on 24 February 2019.
  - Admission to A&E on 04 June 2019 having experienced rigors, vomiting, one episode of diarrhoea for which the patient was hospitalised and nausea.

There were also examples of significant medical history and concomitant medication included in these patient records which had not been entered into the study EDC.

As the MAH did not conduct any monitoring visits apart from the site initiation visit (SIV) and close out visit as per the [redacted] (last signed 19 November 2019), there was no assurance that complete safety information was collected regarding the objectives specified in the study protocol for the other 18 patients enrolled at this site or at other investigator sites in the [redacted] study.

While the SIV for site [redacted] on 01 July 2015 covered source documents, the discussion appeared to have been limited to the availability of patient clinical notes for audits or monitoring visits, and the use of site-specific workbooks to support the data collection. The SIV training slides (undated) did not include clear instructions regarding the identification and location of relevant source documentation to obtain study-relevant information.

Ultimately, this impacted on the completeness and accuracy of the information presented and analysed in the final study report that was submitted to competent authorities on 22 December 2020. Section 12.2 *Adverse Events*, of the final study report stated that 216 out of 556 enrolled patients experienced at least one systemic adverse event, of which five were considered to be related to [redacted] (two serious, three non-serious). However, it was not possible to determine how the accuracy of these figures was ensured due to the lack of quality checks between source documentation and data entered in the EDC.

Post-inspection request 1: As part of the responses to the inspection report, Alimera is requested to address the following points:
1. Evaluate the extent of the critical finding across all 47 investigator sites

2. Retrospectively collect missing information on systemic adverse events from patient records (this may be restricted to sites where full hospital records were not part of the study source documentation at all).
3. Complete supplementary safety evaluation based on the updated dataset. MHRA will inform the PRAC rapporteur for [redacted] of the critical inspection finding and confirm with the MAH whether the supplementary data analyses to the final study report should be submitted to relevant competent authorities.

Post-inspection request 2: As it is envisaged that the above actions will require significant time to complete, periodic CAPA progress reports should be submitted to MHRA. The frequency of the CAPA updates will be agreed once Alimera's formal response to the inspection report has been received.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	
Preventative Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	

Finding CR.1 b)
There were examples of adverse events documented within the ophthalmology patient files that had not been entered into the EDC by site [redacted] and for which no documented assessment was available whether they met the reportability requirements as per the study protocol: • Patient [redacted] received [redacted] in the left eye on 15 April 2015. At a patient routine care visit on 18 December 2018, which was conducted outside of study follow-up visits,

the clinic notes documented that the patient had decreased visual acuity in the right eye with no apparent explanation, but which may have been caused by coincidence or microvesicles. The deterioration in the right eye continued, as documented in the clinic notes for the routine follow-up study visit on 25 February 2019. This decrease in visual acuity in the right eye was not documented within the EDC as an adverse event.

- Patient [redacted] received [redacted] in the left eye on 20 November 2015 and in the right eye on 11 March 2016. As stated in a clinic letter to the patient's GP regarding a clinic visit on 15 August 2016, the patient had neovascularisation in both eyes which was addressed with pan retinal photocoagulation. The PI explained that this patient had previously had neovascularisation prior to entering the study, which increased following implantation of [redacted] Although the procedure was appropriately documented within the EDC under 'Concurrent Ocular Procedures', the PI agreed that the worsening neovascularisation observed on 15 August 2016 should have also been documented in the EDC as an adverse event.

- Patient [redacted] received [redacted] in the left eye on 04 November 2016. During the routine 12-month study visit, the cup-to-disc ratio was measured as 0.7, an increase to the previous visit and considered to be above-normal range. The same result was measured at the 18-month and 24-month visit, but at the 30-month visit the cup-to-disc ratio increased to 0.8. None of these increases had been recorded in the EDC as an adverse event.

- Patient [redacted] received [redacted] in the left eye on 17 August 2017. The patient records stated "unwell" for an unscheduled visit on 16 January 2017. In addition, the notes stated for an unscheduled visit on 27 March 2018 decreased visual acuity and "? ischaemic". A GP letter dated 03 August 2018 also described "retinal ischaemia and R2 features" for the left eye.

- Patient [redacted] received [redacted] in the left eye on 03 February 2016. The patient notes dated 09 December 2016 referred to an episode of vitreous haemorrhage in the non-treated right eye which was resolving. A GP letter dated 12 December 2016 also included this AE. There was no information in the source data whether the event was considered to be reportable or not in accordance with the study protocol. In addition, an entry from 14 March 2019 in the patient records stated that the "patient complains about symptoms in the [right] eye (blurry vision/ glare) -> on waiting list for [right] phaco[emulsification] + IOL".

The [redacted] section 14. *Serious Adverse Events* included a note to file dated 16 March 2022, two years after the investigator site had been closed, stating: [redacted] The note further stated that patients [redacted] were affected and that [redacted]

Root Cause Analysis

[redacted]

[redacted]

Further Assessment
[redacted]
Corrective Action(s)
[redacted]

Deliverable(s)	Due Date(s)
[redacted]	
Preventative Action(s)	
[redacted]	
[redacted]	

C.4.2 Major findings

MA.1 Management and reporting of adverse reactions

Requirements:

Reporting requirements of Individual Case Safety Reports (ICSRs) applicable to marketing authorisation holders during the interim period (EMA/411742/2015 Rev. 9, 29 June 2015), Table 1

Marketing authorisation procedure	Origin	Adverse reaction type	Destination	Time frame
• Centralised • Mutual recognition, decentralised or subject to referral • Purely national	EU	All serious	• Member State where suspected adverse reaction occurred (a)	15 days
		All non-serious	• Member State where suspected adverse reaction occurred, if required (b)	90 days
	Non-EU	All serious	• EudraVigilance database • Member States where suspected medicinal product is authorised, if required (b)	15 days

The Human Medicines Regulations 2012 (SI No. 1916) (as amended), Regulation 188(1)(b)

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 1, effective 16 September – 21 November 2017)
VI.B.2. Validation of reports
"For solicited reports of suspected adverse reactions (see VI.B.1.2.), where the receiver disagrees with the reasonable possibility of causal relationship between the suspected medicinal product and the adverse reaction expressed by the primary source, the case should not be downgraded to a report of non-related adverse event. The opinions of both, the primary source and the receiver, should be recorded in the ICSR."

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2, effective since 22 November 2017)
VI.B.4. Data management
"When transfer of pharmacovigilance data occurs within an organisation or between organisations having set up contractual agreements, the mechanism should be such that there is confidence that all notifications are received; in that, a confirmation and/or reconciliation process should be undertaken."

VI.B.5. Quality management
"[…] marketing authorisation holders should have a quality management system in place to ensure compliance with the necessary quality standards at every stage of case documentation, such as data collection, data transfer, data management, data coding, case validation, case evaluation, case follow-up, ICSR submission and case archiving"

VI.C.1.2.1.1. Non-interventional post-authorisation studies with a design based on primary data collection
"*Information on all adverse events should be collected and recorded from healthcare professionals or consumers in the course of the study unless the protocol provides with a due justification for not collecting certain adverse events. […] For all collected adverse events, comprehensive and high quality information should be sought in a manner which allow for valid ICSRs to be submitted within the appropriate time frames.*"

VI.C.6.2.2.10. Data protection laws
"Pseudonymisation or the use of the nullFlavor 'MSK' should be applied without impairing the information flow in the EudraVigilance database and the interpretation and evaluation of safety data relevant for the protection of public health; given the high-level nature of the information, data elements such as patient's age, age group and gender should in principle be kept un-redacted/visible."

Commission Implementing Regulation (EU) 520/2012, Article 27
"Individual case safety reports shall be used for reporting to the Eudravigilance database suspected adverse reactions to a medicinal product that occur in a single patient at a specific point in time."

The following findings were noted in relation to management and reporting of adverse reactions from the [redacted] study:

Finding MA.1 a)

There were several examples of ICSRs that had not been reported to the MHRA despite meeting the minimum criteria for validation:

- [redacted] cataract extraction in the patient's right eye was entered in the eCRF on 03 January 2017. This was assessed by the investigator as serious and related; however, since the patient was treated with [redacted] in the left eye the MAH assessed this report as not related. The ICRS was therefore not submitted to MHRA.

- [redacted] duodenitis, atrophic gastritis and intestinal metaplasia were initially entered in the eCRF on 04 July 2016 with all events assessed as serious but not related by the investigator. On 01 September 2016, the investigator updated the causality assessment for all three events to suspected relationship to the study treatment. This was reflected in the safety database; however, the ICSR was not reported to the MHRA as the MAH had assessed this report as not related.

- [redacted]: cataract (suspected, not serious) and cataract operation (suspected, serious) were initially entered in the eCRF on 25 October 2016 and 20 February 2017, respectively. After addition of the serious, suspected event, the ICSR was not reported to MHRA as the MAH had assessed both events as non-suspected as they had occurred in the untreated eye.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

[redacted]

Corrective Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	
Preventative Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	

Finding MA.1 b)
Non-serious ADRs of "*increased DMO due to lack of* [redacted] *effect*" were only received by

Alimera on 08 January 2018 even though they had been first entered into the EDC on 24 August 2017. The reports were processed as cases [redacted] and [redacted] and related to patient [redacted] who had experienced several non-serious episodes of "*increased DMO due to lack of* [redacted] *effect*" (also refer to finding MA.1 e)). These were assessed as related by the investigator.

As a result, [redacted] and [redacted] were only reported to EudraVigilance on 27 March 2018 and on 05 April 2018, respectively, seven months after the reactions were first entered into the EDC. Alimera explained in writing during the inspection [redacted]

Post-inspection request: As part of the inspection report response, Alimera should investigate why these cases did not appear in the weekly line listing and assess how many other cases from the [redacted] study were affected.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.1 c)

Day 0 for non-serious ADRs from the [redacted] study had been incorrectly defined as the date the weekly line listing of non-serious adverse events was extracted from the study EDC, rather than the date the ADRs were entered into the EDC. In some cases, this lead to the late submission of non-serious ICSRs to EudraVigilance. For example:

- [redacted] the non-serious, related event of increased intraocular pressure was entered into the EDC on 24 April 2018 and retrieved via line listing on 30 April 2018. The ICSR was submitted to EudraVigilance on 03 August 2018 when it should have been submitted by 23 July 2018.

- [redacted]: the non-serious event of increased intraocular pressure was initially entered into the EDC on 05 October 2018 as not related but was updated to related on 09 October 2018. The report was retrieved via line listing on 15 October 2018. The ICSR was submitted to EudraVigilance on 08 January 2019, one day after the submission due date on 07 January 2019.

- [redacted] the non-serious, related event of "increase in macular oedema" was added to the EDC on 30 July 2018, but company receipt date was captured as 06 August 2018. There was no impact on the timeliness of regulatory reporting as the ICSR was submitted to EudraVigilance within 90 days on 04 September 2018.

- [redacted] the non-serious, related event of increased intraocular pressure was entered into the EDC on 28 September 2018, but company receipt date was captured as 01 October 2018. There was no impact on the timeliness of regulatory reporting as the ICSR was submitted to EudraVigilance within 90 days on 19 December 2018.

This approach did not take into account that the information was provided in the EDC by the site and thus also available to Alimera from that day onwards. Therefore Day 0 should be designated from when this information was entered into the EDC.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)

[redacted]

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.1 d)

There were examples of discrepancies in adverse event reports between the clinical trial database and the global safety database which had been received from the [redacted] study.

i. Serious adverse events were present in the global safety database but were missing in the EDC, thus impacting on the completeness and accuracy of the final study report as it was based on data extracts from the study EDC:

- [redacted] for patient [redacted] listed the serious ADRs of trabeculectomy, increased intraocular pressure as well as the serious event of scleral operation (causality stated as not reported). The event of scleral operation was received as follow-up information to the original case on 21 October 2017 from an Alimera Medical Science Liaison (MSL) who had been sent this information by the prescriber but independently from the [redacted] study.

  The additional adverse event term in the safety database was identified during SAE reconciliation on 09 November 2017 and the CRO Aibili was instructed to notify the investigator site of the additional AE. This was done by Aibili on 13 November 2017 via e-mail, but the correspondence did not include instructions to the site to add the procedure to the eCRF. As request was not raised as a query in the EDC, the was no traceability to ensure action was taken. Protocol section 11.3.2 defined the additional serious events that required reporting "*Serious ocular adverse events include the following: - Any ocular surgical intervention (e.g., cataract surgery, glaucoma surgery).*"

- For patient [redacted], the serious ADR of glaucoma was received spontaneously from the investigator site via an MSL independently from the [redacted] study on 29 December 2017. The ADR was added to case [redacted] which already included the non-serious events of off-label use and intraocular pressure increased, initially received on 02 March 2017. However, the corresponding EDC pages for this patient did not include the serious reaction of glaucoma. During the inspection, Alimera stated that [redacted]

ii. Changes made in the clinical database by investigators were not reflected in the global safety database:

- [redacted] for patient [redacted] included the serious events of vitreous haemorrhage (reporter not suspected, company suspected) and exposure keratitis (reporter not suspected, company not suspected), and the non-serious event of intraocular pressure increased (reporter not suspected, company

suspected). In addition, the safety database case also included the serious event of vitrectomy (reporter causality listed as not reported, company causality suspected); however, this event had not been reported as a standalone SAE in the study EDC but was initially only included in the event description for AE#2 "Vitreous Haemorrhage resolved by vitrectomy" that was entered on 02 March 2017 (after the case was upgraded from non-serious to serious). The eCRF was updated on 08 March 2017 and the event description was changed to "Vitreous Haemorrhage resolved without treatment". The PT of vitrectomy should therefore have been removed from the safety database.

- [redacted] reported retinal neovascularisation, which was initially entered as a serious, related AE into the EDC on 18 August 2016 and coded as such in the safety database. The investigator site changed their assessment to non-serious, unrelated on 18 and 19 August 2016 but this change was not reflected in the safety database subsequently. The initial serious, related ICSR had not been submitted to MHRA despite meeting the minimum reporting criteria.

- [redacted] contained the non-serious event of increased intraocular pressure that was initially entered in the eCRF on 02 November 2018 and retrieved during the weekly review of non-serious AEs on 05 November 2018. As no relatedness assessment had been made by the investigator at that point, this information was not captured in the global safety database. The investigator updated the EDC with the causality assessment of suspected on 06 November 2018; however, the structured field for reporter causality was still listed as "not reported" in the safety database at the time of the inspection. The ICSR was reported to EudraVigilance 08 January 2019.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

[redacted]

Preventative Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.1 e)

Cases [redacted] and [redacted] incorrectly amalgamated independent episodes of increased [redacted] for patient [redacted] into one ICSR by adding new episodes as follow-up to the initial report (refer to MA.1 b)):

- Case [redacted] included episodes of "*increased* [redacted] *due to lack of* [redacted] *effect*" that had been entered separately in the EDC and occurred on the following dates for the left eye:
  - [redacted]: 30 March to 20 July 2017, entered 24 August 2017
  - [redacted]: 07 September to 10 October 2017, entered 20 December 2017
  - [redacted] 14 November 2017 – ongoing, entered 20 December 2017
  - [redacted]: 09 January 2018 (start and end date), AE term added on 26 July 2018
- Case [redacted] ncluded episodes of "*increased* [redacted] *due to lack of* [redacted] *effect*" that had been entered separately in the EDC and occurred on the following dates for the right eye:
  - [redacted] 12 June to 20 July 2017, entered 24 August 2017:
  - [redacted]07 September to 10 October 2017, entered 20 December 2017

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	
Preventative Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	

Finding MA.1 f)

The following quality issues were identified with cases in the safety database that originated from the [redacted] study:

i. For cases [redacted] and [redacted] no reporter and company causality were entered in the [redacted] structured data fields but were only recorded in the narrative. After data migration to [redacted], which was hosted by PrimeVigilance, these fields therefore appeared blank. While a quality check was conducted at the time of initial data entry, causality was not reviewed as part of the checklist. For both cases, causality was assessed as not related by the investigator and the MAH.

ii. No expectedness assessment was completed for seven events in four cases [redacted] nitially received in 2014.

Procedure [redacted] effective until 13 February 2015) stated that the drug safety associate (DSA) was responsible for reviewing "*the information to determine whether the ADE [adverse drug event] is labelled (expected) or unlabeled (unexpected). The DSA uses the most recently approved product labelling archived in the electronic Document Management System*".

Alimera explained during the inspection that expectedness assessments in the safety database would be included in the data outputs provided for the preparation of PSURs.

iii. The following deficiencies were identified with regards to patient birth date information in the safety database:

a. The patient birth date was not entered into the global safety database and structured ICSR fields "patient birth date" and "patient onset age" for several cases even though the patient birth year was available in the study EDC. For example:
   - [redacted] submitted to MHRA on 01 February 2017
   - [redacted] submitted to MHRA on 27 February 2017
   - [redacted] submitted to MHRA on 28 February 2017.

b. The patient birth date was only included in the case narrative in the global safety database and in the ICSR submitted to competent authorities, rather than the structured data fields:

- [redacted] submitted to EudraVigilance on 19 December 2018 and 18 March 2019
- [redacted] submitted to EudraVigilance on 02 August 2018
- [redacted] submitted to EudraVigilance on 08 January 2019.

The MAH stated in writing "*All three cases were processed as per procedure effective at that time* [redacted] *According to this procedure, 'protect confidentiality of the patient and reporter' should always be ticked when manually scheduling reports. This is the reason why the patient age was not visible in the structure E2B field. The current standard PrimeVigilance approach is described in the procedure* [redacted] *where it is stated that this field should not be ticked unless there are data in the case which should not be transmitted.*"

c. For case [redacted] the patient age displayed in the line listing provided for the purposes of the inspection was 0 months. According to the EDC, the patient was born in 1942. The case did not quality for regulatory submission as it only contained non-serious events and was received before November 2017.

iv. The [redacted]' field in the safety database was not completed for 541 cases received between 2014 and 2018. The [redacted] Database Entry Guidelines (versions effective since 22 November 2017) described that this field should be completed; however, it is noted that it was not a mandatory E2B field. The missing dates had no impact on inclusion of these cases in outputs for downstream pharmacovigilance activities, such as PSURs, or on regulatory reporting.

Root Cause Analysis

[redacted]

[redacted]

Further Assessment
[redacted]

Corrective Action(s)
[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)
[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

MA.2 Auditing of the pharmacovigilance system

Requirements:

GVP Module IV – Pharmacovigilance audits (effective 13 December 2012 – 11 August 2015) and Rev 1 (effective since 12 August 2015)
IV.B.2. The risk-based approach to pharmacovigilance audits
"*Risk can be assessed at the following stages:*

- *strategic level audit planning […]*
- *tactical level audit planning […]*

Risk assessment should be documented appropriately for the strategic, tactical and operational planning of pharmacovigilance audit activity in the organisation"

IV.B.2.1. Strategic level audit planning
"*The audit strategy is a high level statement of how the audit activities will be delivered over a period of time, longer than the annual programme, usually for a period of 2-5 years. The audit strategy includes a list of audits that could reasonably be performed. The audit strategy is used to outline the areas highlighted for audit, the audit topics as well as the methods and assumptions (including e.g. risk assessment) on which the audit programme is based.*"

IV.B.2.3.2. Reporting
"*The findings of the auditors should be documented in an audit report and should be communicated to management in a timely manner.*"

IV.B.3.1.2. Qualifications, skills and experience of auditors and continuing professional development
"*Auditors should demonstrate and maintain proficiency in terms of the knowledge, skills and abilities required to effectively conduct and/or participate in pharmacovigilance audit activities. The proficiency of audit team members will have been gained through a combination of education, work experience and training and, as a team, should cover knowledge, skills and abilities in:*

- *audit principles, procedures and techniques;*
- *applicable laws, regulations and other requirements relevant to pharmacovigilance;*
- *pharmacovigilance activities, processes and system(s);*
- *management system(s);*
- *organisational system(s).*"

IV.C.1.1.1. The qualified person responsible for pharmacovigilance in the EU (QPPV)
"*the QPPV should receive pharmacovigilance audit reports*"

GVP Module I – Pharmacovigilance systems and their quality systems
I.C.1.5. Quality system requirements for pharmacovigilance tasks subcontracted by the marketing authorisation holder
"*Further, they [contractual arrangements] should indicate which processes are in place for checking whether the agreed arrangements are being adhered to on an ongoing basis. In this respect, regular risk-based audits of the other organisation by the marketing authorisation holder or introduction of other methods of control and assessment are recommended.*"

GVP Module II – Pharmacovigilance system master file (Rev 2)
II.B.4.7. PSMF section on quality system - Auditing
"*This list should describe the date(s) (of conduct and of report), scope and completion status of audits of service providers, specific pharmacovigilance activities or sites undertaking*

pharmacovigilance and their operational interfaces relevant to the fulfilment of the obligations in the Directive 2001/83/EC, and cover a rolling 5 year period."

Finding MA.2 a)

Alimera's audit strategy was documented in [redacted] Version [redacted] of the document was made effective on 22 July 2021 but it did not contain any information on the planned timeframes within which the specified pharmacovigilance activities, service providers and business partners would be audited.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.2 b)

Alimera did not have any documented risk assessment that supported the annual audit plan and pharmacovigilance audit strategy.

For example [redacted] effective from 27 February 2017 to 22 July 2021) listed the planned audit dates for pharmacovigilance activities carried out in the UK and US, service providers as well as distributors and license partners between 2017 and 2022, but there was no documentation available demonstrating the criteria and thresholds applied to determine the order of audits.

In addition, the annual audit plan was revised on a yearly basis and discussed at the safety meetings between Alimera and PrimeVigilance, which were also attended by the QPPV. Alimera described verbally during the inspection that the topics included on the audit plan were considered to be the highest risk and had therefore been included. However, there was no documentation demonstrating which criteria and thresholds had been applied in the risk assessment to include specific processes and partners in the annual audit plan. For example, the audit strategy stated that the pharmacovigilance activities carried out in the UK and the service provider Regulatop were due to be audited in 2019, but the annual audit plan did not

include either of these topics and there was no rationale stated for their exclusion.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]

Preventative Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.2 c)

Pharmacovigilance audits conducted during the course of the [redacted] study did not fully comply with the requirements outlined in GVP Module IV:

i. Audit conducted of the Alimera Drug Safety function on 19 June 2015:
   - The auditor did not appear to have any relevant experience of the applicable laws, regulations and other requirements relevant to pharmacovigilance or pharmacovigilance activities, processes and systems as he appeared to be a specialist in GMP requirements.
   - The audit report was not shared with the QPPV.

ii. Audit conducted of the CRO Aibili on 09 – 10 September 2019:
   - The auditor did not appear to have any relevant experience of the applicable laws, regulations and other requirements relevant to pharmacovigilance or pharmacovigilance activities, processes and systems as she was a GCP auditor.
   - The audit report was not shared with the QPPV.

Root Cause Analysis

[redacted]

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.2 d)

The contracts and agreements* in place between Alimera and Aibili, the CRO for the [redacted] study did not include any provisions for audit. In addition, Aibili was also not included in the audit strategy documented in [redacted] effective from 27 February 2017 to 22 July 2021).

[redacted] (effective 31 May 2013), and associated [redacted]

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.2 e)

PSMF Annex [redacted]

(version [redacted], effective date 05 July 2021) did not include all information as required by GVP Module II.

i. The "Pharmacovigilance and complaint" audit, conducted on 12 November 2018 and 18 November 2018 audit was not included in the annex.

ii. Information regarding the dates the audit was conducted and reported was missing for the following audits:

- Missing audit dates and missing date of audit report
  - SDEA Management audit. Alimera stated during the inspection that this audit was conducted on 31 March 2019, but it is noted that the annual audit plan only listed an SDEA Management audit for Q1 2018 (with no further information).

- Missing audit end date and missing date of audit report
  - PV training of all Alimera Employees (02 March 2017)
  - EU PSUR/PBRER Management (10 March 2017)
  - Clinical Account Specialists AE training (10 October 2017)

- Missing date of audit report
  - PV audit (20 to 22 September 2016)
  - ICSR handling, processing and reporting (Case Management) (21 June 2018)

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

MA.3 Data management

Requirements:

Commission Implementing Regulation (EU) No. 520/2012
Article 36(3) *"The marketing authorisation holder shall ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information and shall ensure that the confidentiality of the records of the study subjects remains protected."*

Finding MA.3 a)

At investigator site [redacted] where AEs and SAEs were entered into the EDC by non-medical staff, i.e. not the PI or a clinical research fellow, there were no contemporaneous records in the patient health records indicating the serious and causality of the event. Instead, it was described during the inspection that the staff making the EDC data entry would only verbally confirm the seriousness and causality with medically qualified staff.

- Patient [redacted] the AEs of "subconjunctival haemorrhage" (non-serious and related, right eye) and "Mild sub conjunctival Haemorrhage" (non-serious and not related, left eye) were entered by non-medical staff on 12 October 2015 and 05 February 2020, respectively, but there were no records in the patient notes supporting these entries. This was compounded by the PI's delayed signature of AE forms in the EDC on 25 March 2020 and 14 February 2020, which confirmed that the correct assessments had been entered into the EDC.

- Patient [redacted] the AE of "subconjunctival haemorrhage secondary to anaesthetic resolving" (15 March - 22 March 2016, right eye) was entered in the EDC by the study coordinator on 05 April 2016 (related, not serious), but the patient files did not include any written documentation of seriousness and causality. This was compounded by the PI's delayed signature of AE forms in the EDC on 30 May 2019.

- Patient [redacted] the event of localised sub-conjunctival haemorrhage was identified on 09 February 2016 and entered into the EDC on 11 February 2016 by the research nurse as related and non-serious). The source records did not indicate the seriousness and causality of the event and there were no other records indicating that these assessments had been confirmed with the PI or other medically qualified staff contemporaneously at the time of initial data entry. The PI only signed off the report in the system on 30 May 2019.

Further examples were seen during the inspection where the PI had signed off AE reports in the EDC with significant delays over several years.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.3 b)

For patient [redacted] at site [redacted] here was a discrepancy between the electronic medical record system [redacted] and paper patient records with regards to the treatment received.

The [redacted] records (dated 19 June 2015 for right eye and 26 August 2015 for left eye) stated that the patients received [redacted] in the respective eyes, which was also included in the corresponding GP letters. However, the patient's agreement to treatment form [redacted] by the PI and signed but undated by the patient) referred to [redacted] treatment in the left and right eye. It was also seen that the inpatient prescription and administration chart (dated 8 June 2015) listed a prescription for [redacted] for both eyes.

During the inspection the PI explained that at the time of the surgery, [redacted] had not yet been added to [redacted] and therefore [redacted] was selected. However, there were no contemporaneous records available that documented these circumstances.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.3 c)

The [redacted] EDC system audit trail functionality was inadequate as follows:

i. The query audit trail functionality of the EDC was not fit for purpose as it allowed queries to be removed from the system by the creator without providing a reason for removal. During the inspection it was identified that 750 queries were removed from

the system without a reason for removal. Alimera explained that a query could be removed by the user who created the query if it was invalid or created by mistake.

ii. The data management plan allowed for pre-queries to be raised in the system which could be accepted by the monitor (and visible to the site) or rejected. It was confirmed that there was no reason required to be recorded for any pre-queries which would be rejected. However, the rejected queries would be visible in the queries Excel export.

iii. The [redacted] EDC system had two types of edit checks as described in the [redacted] version [redacted] dated [redacted] The first type would fire and allow data to be saved in the form and the second type which would not allow the data to be saved. It was confirmed that only once a form was saved it would be committed to the audit trail and tracked for the initial entry and any data changes. However, for those edit checks that prevented a form from being saved, initial entries would not be visible in the audit trail in order to verify which initial value was entered and then subsequently changed. A review of the edit check specification was performed during the inspection and most of these edit checks which would prevent a form from saving were logical date checks in reference to baseline data.

iv. Sites were not provided with a full audit trail of their CRF data at the end of the study. Queries and the site responses did not appear within the audit trail of the subject data pdfs provided to sites and query reports were not provided separately. The audit trail in the data pdfs contained data changes with a reason 'query resolution' however, the details explaining the change were not available in the audit trail.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Preventative Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.3 d)

The following deficiencies were identified in relation to access control to the [redacted] EDC:

i. Five non-site staff (employed by [redacted]) had edit rights to the [redacted] eCRF which had

not been removed once migration was complete and prior to sites being granted access. This created the potential for non-site staff to edit the investigator's entered data.

Migration of EDC data from the [redacted] system to the [redacted] system took place in 2015 ([redacted] system went live 26 March 2015). During this time the data contained within [redacted] for 63 patients was manually entered into the [redacted] system by contracted data management staff. Staff [redacted] and [redacted] were granted access on 27 March 2015 which was not removed by the end of the study. They made 4198 and 90 entries, respectively, in the eCRF. Alimera confirmed that the data was entered by [redacted] and [redacted] between 30 March 2015 and 10 April 2015 and sites started entering data from 15 April 2015. However, as the [redacted] system audit trail was not available in Excel, it was not possible for the inspector to verify this. It is acknowledged that there was a QC process as part of the data migration which would have mitigated the risk during the migration phase, but there was a lack of control to prevent further changes by not removing staff access once the migration was complete.

ii. Access to the study EDC was not revoked for the staff at investigator site [redacted] that were only temporarily working on the [redacted] study as per the delegation log:

- Research fellow [redacted] worked on the study between 05 September 2016 – 01 October 2017. The staff had access from 31 August 2016, prior to having completed EDC training on 05 September 2016. The last data entry was made on 20 September 2017.
- Research fellow [redacted] worked on the study between 03 November 2017 – 31 July 2019. EDC access granted on 23 November 2017, but never revoked. The last data entry was made on 26 June 2019.
- Study coordinator [redacted] worked on the study between 02 March 2017 – 01 October 2018. EDC access granted on 03 March 2017 but never revoked. The last data entry was made on 29 June 2018.

While no evidence was found that staff had entered data after leaving the study, this is another example of the lack of control to prevent unauthorised changes.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]

Preventative Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.3 e)

There was no evidence available from the EDC system audit trails of which data extractions

had taken place during the study.

Since the [redacted] was finalised (version [redacted], 14 April 2020) prior to database lock and not prior to the start of the study, there was potential for bias to be introduced to this open label study if data was extracted and analyses were performed outside of a formalised plan. During the inspection, Alimera were unable to provide sufficient documentation to demonstrate that no extractions had taken place prior to [redacted] finalisation

Alimera confirmed that there was no evidence that version [redacted] of the [redacted] (dated [redacted] had ever been finalised. It is also noted that a data extraction did take place from the [redacted] EDC system at the time of migration to the [redacted] EDC system in March 2015).

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Preventative Action(s)

[redacted]

Deliverable(s)	Due Date(s)
[redacted]	

Finding MA.3 f)

The following deficiencies were identified in relation to data validation checks in the [redacted] study:

i. There was a discrepancy between the [redacted] dated [redacted] and [redacted] The monitoring plan referred to monthly data validation checks by data management, however the data management plan referred to data checks in the statistical software [redacted] every second month.

ii. There was no documentation available demonstrating that data validation activities had occurred if no queries were required to be raised following the review. Alimera explained that data validation activities were visible from the query report as pre-queries raised. As such there was no positive affirmation of when a review had taken place that did not require any queries to be raised and it could be not confirmed whether data validation checks were performed in October - December 2018 and January 2020.

Root Cause Analysis

[redacted]

Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]

Finding MA.3 g)
The following deficiencies were identified in relation to the remote monitoring activities in the [redacted] study: i. Remote monitoring using the data management tracker were replaced with eCRF manual checks following a decision on 23 November 2016. However, the eCRF [redacted] (version [redacted] was not finalised until 07 October 2019, nearly three years later. ii. There were gaps in the frequency of documented data management reviews of the eCRF data. Evidence of remote monitoring performed for UK sites using the [redacted] were only available for 2016 and early 2017 for the following sites: • [redacted] - provided for 2016 only • [redacted] - provided for 2016 only • [redacted] - provided for 2016 only • [redacted] - provided for 23 February 2016 – 23 March 2017 [redacted] (effective 17 March 2015 – 06 March 2019) and [redacted] (effective from 06 March 2019) stated that "*Data Management will also perform quality checks (QC) of data entered into the system on at least a monthly basis, checking the consistency and completeness of the data.*"
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Preventative Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**

[redacted]

MA.4 Record management

Requirements:

Commission Implementing Regulation (EU) No. 520/2012, Chapter II
Article 12(1)
"*Marketing authorisation holders shall put in place a record management system for all documents used for pharmacovigilance activities that ensures the retrievability of those documents*"

Article 12(2)
"*Pharmacovigilance data and documents relating to individual authorised medicinal products shall be retained as long as the product is authorised and for at least 10 years after the marketing authorisation has ceased to exist.*"

GVP Module I – Pharmacovigilance systems and their quality systems
I.B.10. Record management
"*The record management system should support:*

- *the management of the quality of pharmacovigilance data, including their completeness, accuracy and integrity;*
- *timely access to all records;*
- *effective internal and external communication; and*
- *the retention of documents relating to the pharmacovigilance systems and the conduct of pharmacovigilance for individual medicinal products, in accordance with the applicable retention periods.*"

Finding MA.4 a)	
Alimera could not provide the source documentation for non-serious, spontaneous case [redacted] hat was received on 01 April 2015 and reported a drug administration error as the [redacted] did not dislodge and remained stuck in applicator needle.	
Root Cause Analysis	
[redacted]	
Further Assessment	
[redacted]	
Corrective Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	
Preventative Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	

Finding MA.4 b)
Evidence of QC of the final study report (dated [redacted] had not been retained even though this was required by the Work Order with Jenniss Research (effective 05 May 2020) and Jenniss procedures. As a result, there was no assurance that this independent review took place. Jenniss SOPs [redacted] and [redacted] required a QC review of figures in the document text, in-text tables and safety narrative to be performed for the study report shell, pre-final study report and final study report prior to sending to Alimera and had an associated QC form in attachment 1.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]

Finding MA.4 c)
There was no evidence available from procedural documentation or the system itself of the date the [redacted] EDC system went live. Instead, a study schedule tracker by data management was provided to show the go-live date was 03 January 2014. However, this could not be verified from a system output or a signed database release form or e-mail which demonstrated contemporaneously when this activity occurred.
Root Cause Analysis
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]

Finding MA.4 d)
No evidence had been retained of whether there were any outstanding queries in the [redacted] EDC at the time of migration and how these were managed in the [redacted] EDC (e.g. whether they were also migrated over). In response to inspection document request [redacted] Alimera stated that all queries were resolved prior to migration but the evidence provided did not support this statement as no verification statement or outputs from the system were provided to verify that this activity had been performed.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)
[redacted]

Finding MA.4 e)
There was no documentation available to explain why the monthly Aibili and Alimera project meetings did not take place in April 2017, September 2017, January 2018, March 2019, July 2018, August 2018, November 2018 and December 2018. Schedule [redacted] (dated [redacted] to the [redacted] (dated [redacted] described in section 4 that monthly teleconferences were due to take place for five years during the course of the study.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)
[redacted]

Deliverable(s)	Due Date(s)

C.4.3 Minor findings

MI.1 Computer system validation

Finding MI.1 a)
The following deficiencies were identified in relation to the validation activities for the study EDC: i. There was no validation summary report available for the initial EDC system used for the study [redacted] A [redacted] dated [redacted] was provided which showed edit check tests performed on the system. The tests were indicated with a tick to show it was performed but there was no corresponding result as to whether it passed/ failed. Evidence of UAT (dated 13 March 2015) was provided; however, there was no resolution completed in the status column for all issues raised. Therefore, it could not be determined whether the system was released in a validated state from the documents provided during the inspection. ii. There was no documented evidence available demonstrating that the testing of the SAE email alert functionality in the [redacted] EDC had been undertaken. Alimera are reminded of the requirement in GVP Module I.B.8. that "*Facilities and equipment which are critical for the conduct of pharmacovigilance (see I.B.11.3.) should be subject to appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose.*"
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]

MI.2 Provision of information to inspectors

Finding MI.2 a)
Source documentation for [redacted] CSRs received prior to 2017 was not readily available during the inspection, leading to delays in the provision of requested records. Alimera had identified after the July 2020 migration of the [redacted] safety database from [redacted] o PrimeVigilance that 425 ICSRs dating from 2006 to 2017 did not have any source data attached. This was documented in a deviation on 19 April 2021, but at the time it was decided that no further action was required. The source data was available in the case files from the superseded safety database but had not yet been extracted and were thus not easily retrievable during the inspection. By the end of the inspection, PrimeVigilance, on behalf of Alimera, had completed the task of extracting all source data and storing it in Alimera's electronic archive repository. Alimera are reminded of their responsibility in relation to inspections to "*always to be inspection-ready as inspections may be unannounced*" and "*to make available to the inspectors any information and/or documentation required for the preparation of the inspection within the deadline given or during the conduct of the inspection*" in accordance with GVP III.C.5.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]

Finding MI.2 b)
The line listing provided for the purposes of the inspection and that contained adverse events received during the [redacted] study did not include complete and accurate information. For example, for cases [redacted] the ICSR submission date to EMA/MHRA was blank although the ICSRs had been correctly reported. This was due to various reasons, for example the submission was not correctly tracked in the safety database or did not display correctly due to migration errors.
Root Cause Analysis

[redacted]	
Further Assessment	
[redacted]	
Corrective Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	
Preventative Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	

MI.3 Monitoring activities

Finding MI.3 a)
The following deficiencies were identified with the study monitoring plan: i. The monitoring plan was not finalised prior to the first site initiation visit (SIV) taking place in the UK, despite the monitoring plan outlining the process for SIVs. Seven SIVs at UK sites had taken place between 04 April 2014 and 19 January 2015 prior to version [redacted] of the monitoring plan being finalised on 17 March 2015. It should be noted that version [redacted] of the monitoring plan had never been finalised or issued. ii. Version [redacted] of the monitoring plan (dated [redacted] made reference to remote/ centralised monitoring activities which were to be performed by Aibili but did not state the frequency or how these were to be documented.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]

Finding MI.3 b)
Monitoring reports were not finalised in accordance with timelines specified in the monitoring plan [redacted] dated [redacted] For UK sites, the following delays were identified: • 19 out of 31 close-out visit (COV) reports were finalised more than five business days after the visit with a range of 12 - 2228 calendar days. 7 out of 31 reports were finalised more than 30 calendar days after the visit. • 17 out of 31 SIV reports were finalised more than ten business days after the visit with a range of 20 - 426 calendar days. 14 out of 31 reports were finalised more than 30 calendar days after the visit. The plan required SIV reports to be finalised within ten business days of the visit. COV visit reports were to be completed with five business days for review by the project manager and sending to the sponsor within a further five days.
Root Cause Analysis
[redacted]

Further Assessment
[redacted]
Corrective Action(s)
[redacted]
[redacted]
Preventative Action(s)
[redacted]
Deliverable(s)	**Due Date(s)**
[redacted]

MI.4 Data management

Finding MI.4 a)
There were examples of adverse events documented within the ophthalmology patient notes but had not been entered into the eCRF in a timely fashion, leading to delayed reporting of AEs to Alimera: • Patient [redacted] received [redacted] in the right eye on 27 April 2016. The site called the patient on [redacted] to arrange an appointment to receive [redacted] and spoke to his wife who mentioned the patient was in hospital (admitted [redacted] discharged [redacted] and too unwell to receive treatment. A call was made again a month later on [redacted] and the wife further explained the patient was suffering muscle weakness and sickness due to recently diagnosed Guillain-Barre-Syndrome which were all documented within the patient notes. The patient was discharged from hospital [redacted] and moved to rehabilitation in another hospital. The discharge letter was received by the study team and SAEs of STEMI, Guillain-Barre-Syndrome and Rectal Sheath haematoma were entered into the EDC on [redacted] However, due to the team being made aware of Guillain-Barre-Syndrome on [redacted] the site should have entered this into the EDC within 24 hours of being made aware in accordance with protocol section 11.3.1. • Patient [redacted] experienced a left residual sub-conjunctival haemorrhage on [redacted] Within the clinic notes, this non-serious, not related event was recorded on [redacted] However, this AE was not entered into EDC until [redacted] almost a year later. In addition, it was also not signed off by the PI in the EDC until [redacted] • Patient [redacted] had fallen and fractured her left acetabulum. The Trauma and Orthopaedic department letter was written [redacted] documenting this incident. The [redacted] attempted to contact the patient as she did not attend the 6-monthly visit in [redacted] and reached the care home where the patient had been moved to. In the notes, the [redacted] had written that the patient was unable to attend the appointment as she could not weight bear and would need hospital transport. The [redacted] noted that they would attempt a further call to schedule a visit, which reached the same outcome. Despite of being aware that the patient had been unable to weight bear since [redacted] the hospital letter of the incident was in [redacted] the non-serious, not related AE of left acetabular fracture was not recorded on the EDC until [redacted] almost six months later. This finding was graded as minor as the adverse events were self-identified by the site and entered into the EDC while the study was ongoing. They were therefore available for Alimera's analysis and for inclusion in the final study report.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) | **Due Date(s)**
[redacted]

Preventative Action(s)	
[redacted]	
Deliverable(s)	**Due Date(s)**
[redacted]	

MI.5 Written procedures

Finding MI.5 a)
There was no formalised procedure in place describing the initiation, management, reporting and oversight of post-authorisation safety studies. A procedure had been drafted [redacted] but was never made effective due to the clinical trial manager leaving the MAH prior to completion. At the time of the inspection, Alimera had no other PASS ongoing, therefore this finding has been graded as minor.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
[redacted]
Preventative Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]

Finding MI.5 b)
The SIV training slides used for investigator sites were not version-controlled or dated. Furthermore, there was no reference to the protocol version used to create them. It could be inferred that these were based on protocol amendment [redacted] as they included a reference to retrospective patients and 800 patients to be enrolled (protocol amendment [redacted] reduced the enrolment number from 800 to 500).
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]

MI.6 Study protocol and final study report

Finding MI.6 a)
Multiple instances were identified where the study protocol and final study report did not accurately reflect the study conduct modalities: i. As part of protocol amendment [redacted] ([redacted]), section 5.1 *Overall Study Design* was not updated to state that the follow-up period was 6.5 years from the date of enrolment of the first prospectively enrolled patient. Instead, this section still referred to a 5-year follow-up period. ii. The final study report (dated [redacted]) referred erroneously to a follow-up period of 6 years from the date of enrolment of the first prospectively enrolled patient in the following sections: • Section 8 *Introduction* • Section 9 *Study objectives* • Section 10.1 *Overall Study Design and Plan* • Section 10.2. *Discussion of Study Design, Including the Choice of Control Groups* • Section 10.4.1. *Treatments Administered*
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]
Preventative Action(s)
[redacted]
Deliverable(s) / **Due Date(s)**
[redacted]

C.4.4 Comments

1. The [redacted] to [redacted] EDC data migration included QC of data entry for a sample of seven subjects. For patient [redacted] included in this sample, there was no positive affirmation or documentation to record that there were no findings specific to this subject. [redacted] undated) did not demonstrate any specific findings for this subject or positive statement that the review was performed, and no findings were identified as it only included the findings for all other subjects.

2. An incorrect email address for reporting SAEs was provided in the [redacted] stated these were to be forwarded to [redacted] rather than the named individuals specified in the SIV reporting slides (dated [redacted]). Alimera confirmed there was no impact as this was the generic email address used for the relevant Aibili department responsible for receipt of SAEs.

iii. There was no evidence available of vendor selection for Jenniss Research and which aspects was reviewed as part of this process (e.g. review of quality system, qualifications etc.). It was explained during the inspection that the vendor was selected due to previously working with the MAH on other Alimera studies.

iv. QC of [redacted] outputs were provided for the final study report. A discrepancy was noted for Table [redacted] at month 21 where the N number in the QC output was 206, yet the final study report stated 207. Alimera are required to respond to this comment and explain how this discrepancy was managed and the impact on the data reported in the final study report.
[redacted]

The following comments relate to investigator site [redacted]

v. The patient records which were used as the source documentation for EDC entries did not explicitly state which method was used to assess visual acuity. The [redacted] stated that the "*site indicated they tend to use the snellon [sic] most commonly in clinical practise [sic]*" with the EDTRS 4m chart being the second favoured chart. In addition, the SIV follow-up letter [redacted] included a reminder that the site should ensure "*that the same procedural method is always used for visual acuity for each patient throughout the study*".

During the inspection, the PI verbally confirmed that all visual acuity measurements were taken using the Snellen chart.

vi. The subject hospital number recorded for patient [redacted] at site [redacted] was incorrectly recorded in the [redacted] when it should have been [redacted]

vii. For patient [redacted] at site [redacted] and the 30-month FU visit (21 February 2019), visual acuity was stated in the source data as "PH 6/18" and "6/36", whereas the entry in the EDC stated VA as "6/12".

SECTION D: CONCLUSIONS AND RECOMMENDATIONS

D.1 Conclusions

The factual matter contained in the Inspection Report relates only to those things that the inspection team saw and heard during the inspection process. The Inspection Report is not to be taken as implying a satisfactory state of affairs in documentation, premises, equipment, personnel or procedures not examined during the inspection. It is recommended that you review whether the inspection findings also apply to areas not examined during the inspection and take appropriate action, as necessary.

The responses to the inspection findings, which include proposed corrective and preventative actions, do appear to adequately address the issues identified. No additional responses are required at this time. When the company has adequately implemented the proposed corrective and preventative actions, the pharmacovigilance system will be considered to be in general compliance with applicable legislation.

D.2 Recommendations

The MAH is encouraged to share this inspection report with relevant service providers to whom it has sub-contracted pharmacovigilance activities. Service providers are reminded that deficiencies that are more broadly applicable to MAHs not subject to this inspection may need to be shared with those affected, such that appropriate CAPA can be derived. The service provider and MAH(s) affected should be able to demonstrate effective assessment and resolution of deficiencies that have been reported during any inspection.

This inspection was referred to the MHRA GPvP Compliance Management Team (CMT) and the Inspection Action Group for GCP and Pharmacovigilance (IAG).

[redacted]

APPENDIX I REFERENCE TEXTS

- The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916) as amended.
- Regulation (EC) No. 726/2004 (Title II, Chapter 3), as amended.
- Commission Implementing Regulation (EU) No 520/2012.
- Guideline on good pharmacovigilance practices (GVP).
- Exceptions and modifications to the EU guidance on good pharmacovigilance practices that apply to UK marketing authorisation holders and the licensing authority.
- EMA/CHMP/ICH/287/1995: ICH guideline E2B (R3) on electronic transmission of individual case safety reports (ICSRs) - data elements and message specification - implementation guide.
- EMA/CHMP/ICH/544553/1998: ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER).
- CPMP/ICH/3945/03: ICH guideline E2D “Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting”.
- CPMP/ICH/5716/03: ICH guideline E2E “Pharmacovigilance Planning”.

APPENDIX II PHARMACOVIGILANCE INSPECTION PLAN

MHRA INSPECTION NUMBER	Insp GPvP 41472/11479781-0003	**INSPECTION TEAM**	[redacted]
PHARMACOVIGILANCE INSPECTION OF	Alimera	**DATES**	20 – 24 September 2021
N.B. the inspection plan may be subject to change in the lead-up to, or during, the inspection			

- This inspection will focus on the management and reporting of the non-interventional post authorisation safety study [redacted]
- The majority of day 1 (Monday) will be a pre-inspection day to review the initial document requests. No inspection 'back room' support is expected from Alimera during this time. At the end of the day, inspectors may submit additional document requests to the company.
- An opening meeting will be held by videoconference on 20 September 2021 (day 1) at 15.30 (BST) which will be led by the lead inspector. The agenda will be as follows:
  - Review of the scope and arrangements for the inspection
  - Alimera are asked to lead a company presentation to cover the following aspects:
    1. Overview of the company, pharmacovigilance system and quality system as well as significant changes to the PV system during the duration of the [redacted] study (max. 10-15 minutes).
    2. Overview of the [redacted] study. The presentation should include a brief summary of the study and its objectives, study milestones, allocation of roles/responsibilities, vendors, significant amendments to the conduct, systems and/or vendors during the study, etc. Appropriate subject matter experts (SME) should be available for this presentation for initial questions from inspectors.
- The remainder of the inspection will consist of remote document review, written requests and ad hoc video/telephone clarifications with SMEs as required. Please ensure that CRO staff are available, where applicable. Please provide a designated contact point who can assist with any ad hoc questions from the inspectors or arrange calls between inspectors and SMEs.
- A closing meeting will be held via videoconference on ~~*24 September 2021*~~ *14 October 2021* (timing to be confirmed) during which feedback on the inspection will be provided to the company. All relevant personnel are welcome to attend the closing meeting.

Topics for review	Personnel (Name & job title)
MAH management and oversight of the [redacted] study • Study set-up (to include but not limited to protocol maintenance, ethics approval, role of the QPPV) • Vendor oversight (to include but not limited to adherence to the master services agreement, workload management, quality assurance, audits, etc.) • Quality systems (to include but not limited to procedural documents, audits, record retention, deviation management, etc.)	**Available personnel for interviews:** **Alimera:** [redacted] VP of Regulatory Affairs, Quality and Pharmacovigilance **(GMT-4)** [redacted] Associate director of Drug safety **(GMT+1)** [redacted] - Director of Clinical Operations **(GMT-4)** [redacted] <*Independent consultant*> – Deputy UK QPPV **(GMT+1)** **PrimeVigilance – PV service provider:** [redacted] EEA/UK QPPV for Alimera sciences **(GMT+2)** [redacted] Associate Director, Quality Management **(GMT+1)** [redacted] – Head of Quality **(GMT+1)** [redacted] Associate Manage, Quality and Compliance **(GMT+1)** **Aibili - CRO** [redacted] Quality Manager Aibili **(GMT+1)** [redacted] Quality Manager Backup Aibili **(GMT+1)**

Study management conduct and oversight • Data collection (including but not limited to procedures for the capture of study data, CRF design and maintenance, site initiation, training of site personnel) • Data management (including but not limited to database quality control, monitoring processes, query resolution) • Study close out activities • Data integrity controls • Data and record retention	**Available personnel for interviews:** **Alimera:** [redacted] Associate director of Drug safety **(GMT+1)** [redacted] Director of Clinical Operations **(GMT-4)** [redacted] *ndependent consultant*> – UK Deputy QPPV **(GMT+1)** **PrimeVigilance – PV service provider:** [redacted] EEA/UK QPPV for Alimera sciences **(GMT+2)** **Aibili – CRO:** [redacted] Quality Manager Aibili **(GMT+1)** [redacted] Quality Manager Backup Aibili **(GMT+1)**

Reporting of study results • Data integrity • Completeness and accuracy of safety data in the final study report • Quality control and assurance processes	**Available personnel for interviews:** **Alimera:** [redacted] Associate director of Drug safety **(GMT+1)** [redacted] Director of Clinical Operations **(GMT-4)** [redacted] <*Independent consultant*> – UK Deputy QPPV **(GMT+1)** **PrimeVigilance – PV service provider:** [redacted] - Project manager and EEA deputy QPPV **(GMT+2)** [redacted] EEA/UK QPPV for Alimera sciences **(GMT+2)** **Aibili - CRO** [redacted] Quality Manager Aibili **(GMT+1)** [redacted] Quality Manager Backup Aibili **(GMT+1)**

Management and reporting of adverse drug reactions from the [redacted] study • Case processing and assessment • Expedited reporting of ICSRs • Reconciliation between the safety and clinical databases	**Available personnel for interviews:** **Alimera:** [redacted] Associate director of Drug safety **(GMT+1)** [redacted] Director of Clinical Operations **(GMT-4)** [redacted] <*Independent consultant*> – UK Deputy QPPV **(GMT+1)** **PrimeVigilance** [redacted] - Project manager and EEA deputy QPPV **(GMT+2)** [redacted] EEA/UK QPPV for Alimera sciences **(GMT+2)** [redacted] – Associate Case Processing Manager **(GMT+2)** [redacted]) – PV Physician **(GMT+2)** [redacted] – Senior Director of Strategy, Data and Database Management **Aibili - CRO** [redacted] Quality Manager Aibili **(GMT+1)** [redacted] Quality Manager Backup Aibili **(GMT+1)**
Alimera should complete the below with the names and job titles of the designated contact point and those staff who will be joining the opening meeting.	

Designated contact point during the inspection:

- [redacted](EAA/UK QPPV, [redacted]
- Shukria Khan (Associate director of drug safety, [redacted]

Opening meeting attendees:

Alimera:

- [redacted] – Alimera VP of Regulatory Affairs, Quality and Pharmacovigilance **(GMT-4)**
- [redacted] – Alimera Associate director of drug safety **(GMT+1)**
- [redacted] - Alimera Regulatory Affairs Manager **(GMT+1)**
- [redacted] – Alimera Director of Clinical Operations **(GMT-4)**
- [redacted]*Independent consultant>* – Alimera UK Deputy QPPV **(GMT+1)**

PrimeVigilance:

- [redacted] – Alimera EEA/UK QPPV for Alimera sciences (PrimeVigilance) **(GMT+2)**
- [redacted] Project manager and Alimera EEA deputy QPPV**(GMT+2)**
- [redacted] – PrimeVigilance Head of Quality **(GMT+1)**

Aibili

- [redacted] Aibili Quality Manager **(GMT+1)**
- [redacted] – Aibili Quality Manager Backup **(GMT+1)**

MHRA INSPECTION NUMBER	Insp GPvP 41472/11479781-0003	**DAY**	1 (remote via MS Teams)
PHARMACOVIGILANCE INSPECTION OF	MAH: Alimera Site: [redacted]) Principal Investigator: [redacted]	**DATE**	28 June 2022

[redacted]

Inspection schedule	Time	Staff to be interviewed/available
Opening Meeting Review of inspection scope and inspection plan	14:00 – 14:30	[redacted] -PI & consultant ophthalmologist - [redacted] [redacted] Specialist research nurse, Ophthalmology [redacted] [redacted] [redacted] - Regulatory Advisor [redacted] [redacted]
Interview with the Principal Investigator To include, but not limited to: • Roles and responsibilities of the Principal Investigator • Study approvals • Subject identification and recruitment • Study conduct • Study oversight, including data collection, entry, and reporting • Training of investigator site staff	14:40 – 15:40	Interviewee(s): [redacted] -PI & consultant ophthalmologist - [redacted] [redacted] – Specialist research nurse, [redacted] [redacted] [redacted] - Regulatory Advisor [redacted] [redacted]

MHRA INSPECTION NUMBER	Insp GPvP 41472/11479781-0003	**DAY**	2 (remote via MS Teams)
PHARMACOVIGILANCE INSPECTION OF	MAH: Alimera Site: [redacted] Principal Investigator: [redacted]	**DATE**	29 June 2022

[redacted]

Inspection schedule	Time	Staff to be interviewed/available
Interview with personnel responsible for data entry To include, but not limited to: • Processes for data collection and data entry • AE/SAE reporting • Query management	10:00 – 11:00	Interviewee(s): [redacted] Specialist research nurse, [redacted] [redacted] [redacted]- Regulatory Advisor [redacted] [redacted]

MHRA INSPECTION NUMBER	Insp GPvP 41472/11479781-0003	**DAY**	3
PHARMACOVIGILANCE INSPECTION OF	MAH: Alimera Site: [redacted] Principal Investigator: [redacted]	**DATE**	30 June 2022
LOCATION	[redacted]	**START TIME**	09:00 arrival for a 09:30 start

[redacted]

Inspection schedule	Time	Staff to be interviewed/available
Document and data review Orientation of trial records and source data, including navigation of the electronic health record with nominated site staff. Please make available all relevant records, e. g. Investigator Site File, patient notes (all parts), EDC access, site specific procedures (if applicable). If so, a list of all patients with paper notes should be provided in advance of the inspection to the inspectors. A sample of notes will be requested so please include any notice period required to retrieve them from archives/stores.	09:30 – 12:00	[redacted] Specialist research nurse, [redacted] One of the above will be around
Lunch	12:00 – 13:00	-
Document and data review Please make available all relevant records, e.g. Investigator Site File, patient notes (all parts), EDC access, site specific procedures (if applicable).	13:00 – 17:00	[redacted] – Specialist research nurse, [redacted]

		One of the above will be around

MHRA INSPECTION NUMBER	Insp GPvP 41472/11479781-0003	**DAY**	4
PHARMACOVIGILANCE INSPECTION OF	MAH: Alimera Site: [redacted] Principal Investigator: [redacted]	**DATE**	01 July 2022
LOCATION	[redacted]	**START TIME**	09:00

Inspection schedule	Time	Staff to be interviewed/available
Document and data review Please make available all relevant records, e.g. Investigator Site File, patient notes (all parts), EDC access, site specific procedures (if applicable).	09:00 – 12:00	[redacted] – Specialist research nurse, [redacted] One of the above will be around
Lunch	12:00 – 13:00	-
[redacted] **review and follow-up session with the Principal Investigator** • Sample patient record review of data entered in [redacted] vs printed records. • Follow-up queries and clarifications based on document review (if required).	13:00 – 14:30	Interviewee(s): [redacted] -PI & consultant ophthalmologist - [redacted] – Specialist research nurse, Ophthalmology [redacted] [redacted] - Regulatory Advisor [redacted]
Document and data review	14:30 – 16:00	[redacted] Specialist research nurse, [redacted]

Please make available all relevant records, e.g. Investigator Site File, patient notes (all parts), EDC access, site specific procedures (if applicable).		[redacted] One of the above will be around
~~*Closing meeting*~~	~~*16:00 – 16:30*~~	~~*All welcome.*~~ ~~*Site staff / Sponsor representatives, including*~~ [redacted]
N.B. Documents will be requested during the inspection. This inspection plan may need to be amended before or during the inspection. Inspectors: [redacted]		

MHRA INSPECTION NUMBER	Insp GPvP 41472/11479781-0003	**DAY**	5
PHARMACOVIGILANCE INSPECTION OF	MAH: Alimera Site: [redacted] Principal Investigator: [redacted]	**DATE**	12 July 2022
LOCATION	[redacted]	**START TIME**	09:00

Inspection schedule	Time	Staff to be interviewed/available
Document and data review Please make available all relevant records, e.g. Investigator Site File, patient notes (all parts), EDC access, site specific procedures (if applicable).	09:00 – 12:00	[redacted] – Specialist research nurse, [redacted]
Lunch	12:00 – 13:00	-
Document and data review Please make available all relevant records, e.g. Investigator Site File, patient notes (all parts), EDC access, site specific procedures (if applicable).	13:00 – 16:00	[redacted] – Specialist research nurse, [redacted]
Closing meeting	16:00 – 16:30	All welcome. Site staff / Sponsor representatives, including [redacted] (senior Research nurse) [redacted] and [redacted] (Respiratory consultant) [redacted]

		[redacted]

N.B.

Documents will be requested during the inspection. This inspection plan may need to be amended before or during the inspection.

Inspectors: [redacted]