Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

PHARMACOVIGILANCE INSPECTION REPORT

Pharmacovigilance System Name: Akcea Therapeutics Ireland Ltd.

MHRA Inspection Number: Insp GPvP 51704/18931374-0001

10 South Colonnade, Canary Wharf, London E14 4PU **T** 020 3080 6000 **E** gpvpinspectors@mhra.gov.uk
www.gov.uk/mhra

Table of Contents

ABBREVIATIONS

ADR	Adverse Drug Reaction
CAPA	Corrective and Preventative Action
CHMP	Committee for Medicinal Products for Human Use
DLP	Data Lock Point
EMA	European Medicines Agency
EU	European Union
EVDAS	EudraVigilance Data Analysis System
FAERS	FDA Adverse Event Reporting System
FDA	U.S. Food and Drug Administration
GB	Great Britain
GVP	Good Vigilance Practice
HA	Health Authority
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
KPI	Key Performance Indicator
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Agency
PAP	Patient Assistance Programme
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit Risk Evaluation Report
PIL	Patient Information Leaflet
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
SmPC	EU Summary of Product Characteristics
SDMP	Signal Detection Management Plan
SOC	Safety Oversight Committee
SOP	Standard Operating Procedure

TFUQ	Targeted Follow-Up Questionnaire
UK	United Kingdom
USA	United States of America

SECTION A: INSPECTION REPORT SUMMARY

Section 40 & 43

Inspection type:	Statutory National Inspection
System(s) inspected:	Akcea Therapeutics Ireland Ltd., [redacted] UK PSMF number not available at the time of the inspection – [redacted] dated 27 May 2021
Site(s) of inspection:	Remote inspection
Main site contact:	Name: [redacted] Address: 2855 Gazelle Court, Carlsbad, CA 92010, USA [redacted]
Date(s) of inspection:	06 – 09 July 2021
Lead Inspector:	[redacted]
Accompanying Inspector(s):	[redacted]
Previous inspection date(s):	N/A
Purpose of inspection:	Inspection of pharmacovigilance systems to review compliance with UK and EU requirements.
Name and location of UK QPPV:	Name: [redacted] Address: PPD, 11/2 Srodkowa Street, 31-436 Krakow, Poland [redacted]
Global PV database (in use at the time of the inspection):	Oracle Argus [redacted] (commercially available)
Key service provider(s):	PPD was contracted to provide global pharmacovigilance services; this included the role of the UK/EU QPPV and deputy, holding the global safety database, case processing and signal detection. ProPharma Group was contracted to provide medical information services.
Inspection finding summary:	2 Major findings 4 Minor findings
Date of first issue of report to MAH:	12 August 2021
Deadline for submission of responses by MAH:	17 September 2021 Updated responses due 30 September 2021
Date(s) of receipt of responses from MAH:	16 September 2021 Updated responses received 30 September 2021
Date of final version of report:	30 September 2021
Report author:	[redacted] Pharmacovigilance Inspector

SECTION B: BACKGROUND AND SCOPE

B.1 Background information

Insert Company NameAkcea) 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. In particular, reference was made to The Human Medicines Regulations 2012 as amended, Regulation (EC) No 726/2004 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.

Section 43

Akcea was formed in 2014 to commercialise products on behalf of Ionis Pharmaceuticals, a pharmaceutical company specialising in RNA therapeutics. In October 2020, Ionis Pharmaceuticals acquired the remaining shares of Akcea [redacted] and Akcea became a wholly owned subsidiary. At the point of acquisition, the two companies held two standalone pharmacovigilance systems. The integration of the two systems was ongoing at the time of the inspection, with a fully integrated pharmacovigilance system planned for December 2021.

Akcea commercialises two products, [redacted] and [redacted] both of which are subject to additional monitoring. The products were centrally authorised in the EU on 06 July 2018 and 03 May 2019, respectively, and the licences have subsequently been grandfathered to GB licences following the exit of the UK from the EU on 01 January 2021.

The company is headquartered in Carlsbad, CA, USA. PPD is contracted to provide global pharmacovigilance services. These services include holding the global safety database, receiving pharmacovigilance data, case entry, processing, and onward submission to regulatory authorities. PPD also has responsibilities in PSUR writing, signal detection, and maintains the role of the UK/EU QPPV and deputy QPPV for Akcea. A vendor governance structure has been established between applicable operational and managerial levels.

B.2 Scope of the inspection

The inspection included a review of specified global pharmacovigilance processes and was performed remotely. No formal interview sessions were scheduled, with the inspection primarily taking the form of document review (including outputs from the global safety database). Ad hoc teleconferences were held with subject matter experts as necessary. The systems reviewed during the inspection are highlighted in the Pharmacovigilance Inspection Plan (attached as Appendix II).

Areas regarding the maintenance of reference safety information and the quality management system were not reviewed in detail and it is recommended that these areas are subject to closer review during a subsequent pharmacovigilance inspection.

Section 43

B.3 Documents submitted prior to the inspection

The company submitted a UK PSMF ([redacted] effective 27 May 2021) 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 sheets A and B.

B.4 Conduct of the inspection

In general, the inspection was performed in accordance with the Inspection Plan.

A closing meeting was held remotely to review the inspection findings on 09 July 2021.

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

Not applicable as this was the first MHRA pharmacovigilance inspection of the company.

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

No critical findings were identified from the review of pharmacovigilance processes, procedures and documents performed during this inspection.

C.4.2 Major findings

MA.1 Written procedures

Requirements:

The Human Medicines Regulations 2012 (Statutory Instrument 2012 No. 1916)
Schedule 12A, paragraph 11(1)

Commission Implementing Regulation (EU) No. 520/2012
Article 11(1)

GVP Module IX – Signal management (Rev 1)
IX.B.5. Quality requirements
"Signal management is considered a critical process (see GVP Module I). Any signal management system should be clearly documented to ensure that the system functions properly and effectively, that the roles, responsibilities and required tasks are clear and standardised, that these tasks are conducted by staff with appropriate qualifications and expertise and that there are provisions for appropriate control and, when needed, improvement of the system. A system of quality management (see GVP Module I) should be applied to all signal management processes. Detailed procedures for this quality system should be developed, documented and implemented. This includes the rationale for the method and periodicity of signal detection activities."

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)
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 […]

Clear written standard operating procedures should guarantee that the roles and responsibilities and the required tasks are clear to all parties involved and that there is provision for proper control and, when needed, change of the system. This is equally applicable to activities that are contracted out to third parties, whose procedures should be reviewed to verify that they are adequate and compliant with applicable requirements."

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."*

At the time of the inspection, the Akcea and Ionis pharmacovigilance systems were undergoing integration and a pharmacovigilance integration plan had been set out to support this transition. As part of these ongoing integration activities, an internal pharmacovigilance SOP review was underway, which had identified that Akcea had limited pharmacovigilance SOPs and was leveraging safety vendor SOPs for pharmacovigilance activities. Until December 2021, when all pharmacovigilance processes were planned to be integrated, Akcea would continue to use Akcea and Ionis SOPs and leverage PPD SOPs for certain pharmacovigilance processes.

The following findings were noted in relation to the MAH's written procedures:

Finding MA.1 a)
Between the period January 2020 – May 2021, there were no effective written procedures supporting the Akcea signal detection and management process. Prior to January 2020, signal management activities had been solely conducted by the service provider, PPD. In January 2020, activities were transferred in-house to Akcea, although PPD retained responsibility for generating summarised signal detection data from the global safety database for Akcea to review, as well as conducting a weekly literature review and periodic monitoring of regulatory authority alerts. It was not until the internal pharmacovigilance SOP review conducted as part of Ionis-Akcea integration activities that it was identified that there were no effective SOPs governing the signal management process being conducted by Akcea. It was confirmed during the inspection that the process previously in place by PPD continued to be followed, and evidence was observed that monthly signal detection activities had been conducted for the two authorised products in this time period. Since May 2021, the Ionis SOP [redacted] 15 July 2019), had been utilised as the procedure for signal detection. Minor deficiencies were identified with this SOP; please refer to finding MI.1b. To note, this non-compliance had not been formally raised in the Akcea quality management system at the time of the inspection.
Root Cause Analysis
[redacted]
Further Assessment
[redacted]
Corrective Action(s)
[redacted]

Section 43

Section 43

[redacted]

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

Preventative Action(s)

[redacted]

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

Finding MA.1 b)

There were no written procedures to support the set up and management of non-interventional PASS sponsored by Akcea.

At the time of inspection, Akcea had two ongoing non-interventional PASS: an RMP category 2 study for [redacted] with UK sites [redacted] for which data collection had started in January 2021, and an RMP category 3 study for [redacted] for which data collection was initiated in May 2021. For the category 2 study [redacted] Akcea had assigned vendors to provide study coordination services [redacted] and support with data management [redacted] According to the respective agreements, Akcea would maintain oversight through mechanisms such as study team meetings with [redacted] (as stated in the Scope of Work Number [redacted] 21 September 2020) and regular teleconferences with [redacted] (as stated in the Statement of Work [redacted], 06 August 2020).

However, there were no written procedures forming part of the quality management system at Akcea to support and facilitate the set up and ongoing management of non-interventional PASS, including any required communication with the licensing authority.

Root Cause Analysis

[redacted]

Section 43

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)
There were no written procedures governing the roles and responsibilities of Akcea personnel involved in case processing activities. Case processing activities had been outsourced to PPD since 2018 and PPD used their own written procedures to complete these activities. However, during the inspection it was confirmed that a further medical review step was conducted by Akcea to ensure appropriate assessment had been completed by PPD (such as confirming an upgrade or downgrade of case seriousness). Serious cases were forwarded to Akcea and weekly listings of non-serious cases were shared with an Akcea physician for review. Although this process was described at a high level in the Safety Management Plan [redacted] 06 September 2019) between PPD and Akcea, there were no written procedures that described Akcea's involvement in case processing activities. PPD's procedures were specific to their own processes for all clients and the Ionis case processing procedure provided during the inspection did not reflect the activities being carried out in practice.
Root Cause Analysis
[redacted]

Section 43

[redacted]

Further Assessment

[redacted]

Section 43

[redacted]

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

MA.2 Management of adverse drug reactions

Requirements:

GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)
VI.B.1.2. Solicited reports
"As defined in ICH-E2D (see GVP Annex IV), solicited reports of suspected adverse reactions are those derived from organised data collection systems, which include clinical trials, non-interventional studies, registries, post-approval named patient use programmes, other patient support and disease management programmes, surveys of patients or healthcare professionals, compassionate use or name patient use, or information gathering on efficacy or patient compliance."

VI.B.3. Follow-up of reports
"*When first received, the information in suspected adverse reactions reports may be incomplete. These reports should be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases. This is particularly relevant for monitored events of special interest, […]. Any attempt to obtain follow-up information should be documented."*

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 […] case follow-up […]*"

VI.C.2.2.11. Reports from patient support programmes and market research programmes
"A patient support programme is an organised system where a marketing authorisation holder receives and collects information relating to the use of its medicinal products. Examples are post-authorisation patient support and disease management programmes, surveys of patients and healthcare professionals, information gathering on patient compliance, or compensation/re-imbursement schemes. […]

Safety reports originating from those programmes should be considered as solicited reports. The marketing authorisation holder should have the same mechanisms in place as for all other solicited reports (see VI.C.2.2.2. for marketing authorisation holders responsibilities on solicited reports) to manage that information and to submit, in line with the time frames and modalities outlined in VI.C.3. and VI.C.4., valid cases of adverse reactions which are suspected to be related to the concerned medicinal product."

Section 43

Finding MA.2 a)

Adverse event reports received from the [redacted] and [redacted] were incorrectly recorded as spontaneous cases in the global safety database rather than solicited cases.

The UK PAP involved regular nurse visits, usually every two weeks for 30 minutes, to take blood samples from the patient. Nurses would also be responsible for informing the patient of the test results and reporting any abnormal results, such as platelet count reduction or blood triglycerides increased, to the medical information provider, ProPharma Group (PPG), as adverse events. Nurses were appropriately trained to identify and report any other adverse events experienced by the patients' enrolled in the study to PPG.

Such a system of organised data collection requires that adverse events arising from enrolled patients are collected as solicited reports. At the time of the inspection, there were 70 cases from [redacted] and [redacted] PAPs in the database. Akcea confirmed that these cases would have been included in the post-marketing ADR summary tabulations as spontaneous reports in previous [redacted] and [redacted] PSURs.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Section 43

[redacted]

Corrective Action(s)

[redacted]

[redacted]

Preventative Action(s)

[redacted]

Section 43

Deliverable(s)	Due Date(s)

Finding MA.2 b)

There were several deficiencies identified with the management of follow-up requests of adverse event reports:

i. There was no evidence to demonstrate that follow-up requests had been sent for the following cases that required a targeted follow-up questionnaire (TFUQ):

- Spontaneous case was received 17 August 2020 from a healthcare professional who reported kidney function deterioration with As per the 30 May 2018), a TFUQ was required for reports of renal events. The case was coded on the database with the serious event of 'renal impairment' but no follow-up was conducted despite the availability of full reporter contact information and permission to contact the reporter.
- Spontaneous case was received 18 November 2019 from a consumer reporting events of *Escherichia* urinary tract infection and eye haemorrhage. As per the 30 May 2018), a TFUQ was required for reports of ocular events. Akcea was unable to provide evidence to confirm that a TFUQ had been sent to the reporter.

ii. Examples were identified where follow-up requests to obtain further information to evaluate reports were significantly delayed:

- Case Non-serious report of a urinary infection following treatment with The case was initially received 20 September 2019; however, follow-up was not attempted until 25 February 2020, 158 calendar days later.
- Case Serious report of device malfunction with a pacemaker following treatment. The case was initially received 03 February 2020; initial follow-up was sent on 13 February 2020 and no response was received. The second follow-up attempt was not sent until 06 July 2020, 143 calendar days later.

At the time of these requests, the PPD SOP was being followed, which required first follow-up attempts to be sent within five calendar days of the receipt date, and second follow-up attempts to be sent two business days after an unsuccessful attempt for requests sent via telephone and fax or two calendar weeks after an unsuccessful attempt for requests sent via mail.

iii. The timelines being adhered to for the follow-up of Akcea adverse event reports were not documented in a written procedure for PPD to use.

Akcea and PPD confirmed that the first follow-up attempt would be scheduled within 15 calendar days from the initial receipt date and further follow-up attempts should be made two calendar weeks apart from each unsuccessful attempt. A total of three attempts would be made for serious unexpected reports and two attempts would be made for serious expected or non-serious reports. These timeframes were

Section 43

established and shared in an email between Akcea and PPD on 24 February 2020. However, the governing SOP held by PPD [redacted] ([redacted] 16 December 2020) described notably different timeframes to conduct initial follow-up, stating that this should be sent out within five calendar days of initial receipt date.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Section 43

[redacted]

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

Finding MA.2 c)

There were deficiencies in the reconciliation processes set up between the Akcea global safety database holder, PPD, and several parties receiving safety data for Akcea-authorised products.

Evidence of PPD initiating the reconciliation process by sending case listings via email to the relevant parties involved in the [redacted] (a clinical study) and the early access programme for [redacted] was obtained during the inspection. However, there were no records demonstrating that the reconciliation process was completed by the parties:

i. The reconciliation process described in the relevant Safety Management Plans between PPD and the parties involved in the [redacted] 20 November 2020) and [redacted] 23 September 2020) did not require

Section 43

any confirmation of receipt or completed reconciliation to be sent back from the party to PPD for assurance that all safety data had been correctly transferred, and no evidence could be provided to demonstrate this.

ii. The Safety Management Plans for [redacted] 30 July 2019) and [redacted] 24 August 2020) stated, *"PPD PV will provide a case listing to Akcea by the first Friday of each month showing all events received by PPD PV. Akcea will reconcile and confirm all expedited safety reports have been submitted to applicable regulatory agencies."* Evidence was observed of the line listings being sent to Akcea, but no such confirmation was provided to PPD for assurance that the check had been completed.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

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

Preventative Action(s)

[redacted]

Section 43

[redacted]

C.4.3 Minor findings

Section 43

MI.1 Quality requirements for signal management

Finding MI.1 a)
The following issues were identified with the Safety Signal Tracking Log, used by Akcea to track all signals for [redacted] and [redacted] i. It was confirmed by Akcea that non-validated signals originating from internal signal detection processes were not added to the signal tracker. This was contrary to [redacted] 15 July 2019), which stated in section 2.2.2 that "*non-validated signal will be closed and documented in the Safety Signal Tracking Log within 10 business days of decision".* ii. The date signals were validated or not validated was not documented on the tracker. The tracker only included the date the signal was first detected and the date the signal was closed; hence it was not possible to trace all steps and decisions taken within the signal management process. iii. Multiple signal actions were inaccurately presented on the signal tracker. The signal tracker for [redacted] ncluded six signals that had been identified through the PRAC assessment reports for [redacted] PSURs. For these signals, the tracker included details on the method of signal evaluation and all actions were stated to be 'refuted signal'. However, it was confirmed by Akcea that these signals were not validated, and this had been inaccurately recorded on the tracker. Additionally, the signal of hypersensitivity, which was raised through the PRAC assessment report to the [redacted] PSUR on 14 December 2020, did not accurately record the final signal action. Although Akcea had initially not validated the signal in the response to the PRAC assessment report, the PRAC assessor disagreed with this assessment and requested that a variation was submitted to update the SmPC and PIL with an appropriate warning regarding the risk. Evidence was provided to show that a variation had been submitted to the EMA and MHRA, despite this not being recorded on the tracker. iv. As per section 3.3 of [redacted] 15 July 2019), signals were prioritised by assigning them a level (Levels 1 – 3), which dictated the timelines for signal assessment, escalation and actions. These levels were not documented on the tracker. The MAH is reminded of the quality requirements outlined in GVP IX.B.5., which state "*Through a tracking system, all organisations should keep an audit trail of signal management activities, allowing traceability (i.e. recording of dates and confirmation of timeliness) and process control of the details of all steps of signal management, including analyses, decisions and rationale*."
Root Cause Analysis
[redacted]

Section 43

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

[redacted]

Preventative Action(s)

[redacted]

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

Finding MI.1 b)

Since May 2021, the Ionis SOP [redacted] 15 July 2019) had been followed by Akcea. The following issues were identified with the current SOP governing signal management activities:

i. The SOP described sources of signal detection data that were not reviewed by Akcea.

- Section 1.3.3 stated "*Retrieve and review safety data from healthcare claims databases and HA databases such as EudraVigilance via EVDAS interface on monthly basis*". However, it was confirmed that data from EudraVigilance were not reviewed for [redacted] or [redacted] (neither products were on the 'List of active substances involved in the pilot on signal detection in EudraVigilance by marketing authorisation holders').
- Section 1.3.4 stated "*Periodically retrieve and review safety data from the FDA Adverse Event Reporting System (FAERS) for products that are marketed in the US*". [redacted] was marketed in the USA; however, data from FAERS were not reviewed.

ii. The signal validation step described in the SOP did not accurately detail the process followed by Akcea.

It was described verbally during the inspection that potential signals would be validated through discussion at the monthly signal review meetings. Alternatively, an ad hoc Ionis Safety Oversight Committee (SOC) meeting could be held. The SOP did not outline these steps, and only stated that the Drug Safety Physician or Drug Safety Manager would "*lead the safety team to complete signal validation to verify if the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association between the Ionis compound and the event, or a new aspect […] of a known ADR*".

iii. The signal prioritisation step outlined in the SOP lacked clarity.

In section 3.2 of the SOP, it stated "*Signal prioritization activities must be completed within 15 business days after the completion of signal validation*". It subsequently stated in section 3.3 that "*the outcome of signal assessment can be Level 1, Level 2, Level 3, or Safety Signal Refuted*" [emphasis added]. These levels were assigned different timelines for completion of signal assessment (either one month or two months after signal prioritisation). It was not clear how either the prioritisation or assessment timelines were adhered to, when the decision to assign signals a level was completed after signal assessment.

Section 43

As an example, the signal of liver transplant rejection with [redacted] was assigned priority Level 2 after the signal was assessed and it was decided that a product label update was necessary. It was confirmed by Akcea in document request J4 that the signal action determined which priority level was assigned, which was contrary to the process described in the SOP.

iv. The signal detection methodology applied by Akcea was not clearly documented to ensure that the required tasks were clear and standardised.

The methodology involved a qualitative real-time review at the medical assessment step of case processing and a qualitative monthly review of aggregate reports for each product. Section 1.3.1 of the SOP provided a high-level overview of the required activities, stating "*Review safety data in the safety database (i.e. real-time SAE review, monthly aggregate safety data review) on an ongoing basis*"; however, the SOP did not provide any further guidance as to how these outputs should be assessed or what constituted a potential signal. It was confirmed verbally that Drug Safety Physicians would review each individual case and focus on serious adverse events and important identified/potential risks. As per the quality requirements outlined in GVP IX.B.5., Akcea should formally document the process steps taken during the qualitative signal review to ensure the required tasks are clear and standardised. This is particularly important should the number of reports received monthly for either product increase.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Section 43

Corrective Action(s)
[redacted]

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

Preventative Action(s)
[redacted]

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

MI.2 Pharmacovigilance agreements

Finding MI.2 a)
The pharmacovigilance contract with the service provider, PPD, had not been updated to reflect a significant change in signal management responsibilities effective since January 2020. Appendix E of the project addendum (14 September 2018) outlined PPD's responsibilities for post-marketing signal detection, evaluation and management. These responsibilities included validation of potential signals with feedback to Akcea prior to undertaking any full signal evaluation, as well as tracking of signals. In January 2020, signal validation, prioritisation, evaluation and tracking responsibilities were transferred to Akcea. The project addendum had been updated since January 2020 on 29 July 2020 (amendment no. 2); however, the amendment did not include any updates to Appendix E of the contract that detailed the signal management activities. Additionally, the Signal Detection Management Plan (SDMP; [redacted] 19 May 2020), which further defined the contracted activities and responsibilities of PPD to support the signal detection and management process at Akcea, did not accurately reflect the current practices. For example, sections II.A.4. and II.A.6. of the SDMP stated PPD was responsible for signal evaluation and tracking, respectively.
Root Cause Analysis
[redacted]

Section 43

[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 Periodic safety update reports

Finding MI.3 a)
Adverse events that had been assessed by the reporter and company as unrelated to the medicinal product were incorrectly included in PSUR post-marketing ADR summary tabulations. It was confirmed by Akcea that the programming assessment used for the summary tabulation in PSURs was calculated at the case level based on the primary event of the case. Therefore, if the primary event met the criteria for inclusion in the ADR tabulation, then all events within the case, irrespective of whether they met the criteria for inclusion, would be included in the ADR tabulation outputs. As an example, the serious events 'myocardial infarction' and 'cerebrovascular accident' from spontaneous case [redacted] which were reported to be unrelated by the reporter and the company, were included in Appendix 2C 'Cumulative and Interval Post Marketing ADR

Section 43

Tabulations' of the [redacted] 02 May 2021), as the primary event 'loss of consciousness' was considered to be related.

Post-inspection request: [redacted]

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

[redacted]

Section 43

[redacted]

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

Preventative Action(s)

[redacted]

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

MI.4 Management of post-authorisation safety studies

Finding MI.4 a)

No monthly medical monitoring reports were provided to Akcea during the first eight months of the [redacted] following the first patient visit milestone in December 2020.

The Medical Monitoring Plan [redacted] 15 September 2020) defined that each month a medical monitoring report would be provided to Akcea by the medical monitor (outsourced to [redacted] in Excel format documenting at a minimum: the number of queries received, the types of queries and any safety issues arising from queries. However, no medical monitoring reports had been provided to Akcea until 07 July 2021, after it was raised on inspection.

No medical monitoring queries were raised between December 2020 and March 2021, and the number of queries logged between April and June 2021 was relatively low; hence, the impact of this finding is not considered to be significant.

Root Cause Analysis

[redacted]

Further Assessment

[redacted]

Corrective Action(s)

Section 43

[redacted]

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

Preventative Action(s)
[redacted]

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

C.4.4 Comments

- [redacted]

[redacted]

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. 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 Lead Inspector has recommended that the next MHRA inspection is performed as part of the routine risk-based national inspection programme.

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.
- CPMP/ICH/377/95: ICH guideline E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting".
- 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

Section 40

MHRA INSPECTION NUMBER	Insp GPvP 51704/18931374-0001	**INSPECTION TEAM**	[redacted]
PHARMACOVIGILANCE INSPECTION OF	Akcea	**DATES**	06 – 09 July 2021

N.B. the inspection plan may be subject to change in the lead-up to, or during, the inspection

- An opening meeting will be held by videoconference at 3pm (BST) on Tuesday 06 July 2021 (to accommodate the distribution of personnel across different time zones), which will be led by the lead inspector. The agenda will be as follows:
  - Review of the scope and arrangements for the inspection
  - Akcea are asked to lead a short company presentation (max. 20 minutes), which aims to provide the inspectors with an overview of the company and pharmacovigilance system. The presentation should focus on the topics listed for inspection and any relevant ongoing remediation work in the pharmacovigilance system.
- The remainder of the inspection will consist of remote document review, written requests and ad hoc video/telephone clarifications with subject matter experts as required. Please provide a designated contact point who can assist with any ad hoc questions from the inspectors or arrange calls between inspectors and subject matter experts as required.
- A closing meeting will be held via videoconference on Friday 09 July 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)
Topic 1 – ADR management To include, but not limited to: • Management and reporting of ICSRs • Case quality in the safety database • Follow-up activities	[redacted] Vice President & Head of Drug Safety, Safety & Pharmacovigilance (PST) [redacted] Drug Safety, Safety & Pharmacovigilance (PST), ICSR intake and assessment [redacted] Executive Medical Director, Safety & Pharmacovigilance (EST), Drug Safety Physician ICSR reviews [redacted] QPPV (CEST)

Section 40

	From PPD for PVG Operations: [redacted] Associate Director Pharmacovigilance (EEST) [redacted] Senior Pharmacovigilance Project Delivery Manager (EEST) [redacted] Manager Pharmacovigilance (EEST) [redacted] Principal Safety Specialist (EEST) [redacted] Principal Safety Specialist (EST) [redacted] Manager Pharmacovigilance Central Safety Reporting (EST) [redacted] Safety Reporting Specialist Central Safety Reporting (EST)
Topic 2 – Periodic safety update reports	[redacted] Vice President & Head of Drug Safety, Safety & Pharmacovigilance (PST) [redacted] Director, Drug Safety, Safety & Pharmacovigilance (PST), Submission [redacted] Executive Medical Director, Safety & Pharmacovigilance (EST), Medical Review [redacted] Director, Pharmacovigilance, Safety & Pharmacovigilance (EST), Production [redacted] Director, Regulatory Affairs, Global Regulatory Lead - Tegsedi (EST)

Section 40

	[redacted] Senior Director, Regulatory Affairs, Global Regulatory Lead - Waylivra (EST) [redacted] QPPV (CEST) **From PPD:** [redacted] Safety Writer III, PSUR Subject Matter Expert (CEST) (Unavailable: Tuesday 6th until 12pm CEST) [redacted] Safety Writer III, PSUR Subject Matter Expert (IST)
Topic 3 – Signal management To include, but not limited to: • Signal detection and evaluation activities • Quality requirements	[redacted] Vice President & Head of Drug Safety, Safety & Pharmacovigilance (PST) [redacted] Director, Drug Safety, Safety & Pharmacovigilance (PST) [redacted] Executive Medical Director, Safety & Pharmacovigilance (EST) [redacted] Director, Pharmacovigilance, Safety & Pharmacovigilance (EST) [redacted] QPPV (CEST) **From PPD as optional presence:** [redacted] Director, Signal detection, (BST) [redacted] Safety Scientist II, Signal detection (IST)
Topic 4 – Sources of safety data To include, but not limited to:	[redacted] Vice President & Head of Drug Safety, Safety & Pharmacovigilance (PST)

Section 40

• Spontaneous sources, including business partners and medical information enquiries • Solicited sources, including non-interventional PASS and patient assistance programmes	[redacted] Director, Drug Safety, Safety & Pharmacovigilance (PST) [redacted] Executive Medical Director, Safety & Pharmacovigilance (EST) [redacted] Director, Pharmacovigilance, Safety & Pharmacovigilance (EST) [redacted] VP, Interim Head Global Medical Affairs, (BST) [redacted] Director, Global Medical Information (EST) [redacted] Executive Director, Clinical Operations, Waylivra post-marketing studies (PST) [redacted] Senior Manager, Clinical Operations, Tegsedi post-marketing studies (EST) [redacted] Therapeutic Area (TA) Strategy Head, Medical Affairs Europe, early access program (BST) [redacted] QPPV (CEST) **ProPharma (Global call center for medical information):** [redacted] Executive Client Account Manager (BST) [redacted] Regional Manager, Client Services (BST) **Sobi (Distribution partner):** [redacted] Medical Affairs Specialist, UK & RoI (BST)

Section 40

Akcea 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]

Opening meeting attendees:

[redacted]

Section 40

[redacted]