Medicines & Healthcare products
Regulatory Agency

Takeda GCP Inspection Report

Inspection No: Insp GCP 16189/19142243-0002

Published 24 April 2025

Contents

Inspection Summary

Inspection & Organisation Information	
Inspection Number	Insp GCP 16189/19142243-0002
Purpose of Inspection	Statutory GCP Systems
Type of Inspection	Remote
Organisation Inspected	Takeda Development Centre Europe Ltd (Takeda)
Organisation Address	1 Kingdom Street, London. W2 6BD
Organisation Type	Commercial
Dates of Inspection	Day 1: 06 June 2024 Days 2 to 6: 10 to 14 June 2024 Total 5 days over 6 days.
Lead Inspector	[redacted] GCP Inspector [redacted]
Accompanying Inspectors	[redacted] [redacted] GCP Inspector [redacted] [redacted] GPvP Inspector [redacted]
Date of Closing Meeting	Initial Closing Meeting Date: 14 June 2024 Second Closing Meeting following further document review: 11 October 2024

Investigator Site 01	
Name of Investigator	[redacted]
Organisation Inspected	Site [redacted] Maidstone Hospital
Organisation Address	Maidstone Hospital, Hermitage Lane, Maidstone, Kent. ME16 9QQ
Organisation Type	NHS Hospital
Protocol Reference	[redacted] A Phase 3, Randomized, Controlled, Open-Label, Clinical Study of [redacted]

	[redacted]
IRAS ID	[redacted]
Dates of Inspection	20 to 22 August 2024
Lead Inspector	[redacted] GCP Inspector [redacted]
Date of Closing Meeting	22 August 2024

Inspection Report Version History (For Inspectorate Use Only)	
Inspection Report Date 01	24 April 2025
Response Receipt Date 01	30 June 2025
MHRA Review Date 01	26 September 2025
Response Receipt Date 02	31 October 2025
MHRA Review Date 02	05 January 2026

Inspection Close Date	05 January 2026

Clinical Trials Reviewed	
Protocol Reference	[redacted]
IRAS ID	[redacted]
Protocol Title	A Phase 3, Randomized, Controlled, Open-Label, Multicenter, Safety and Efficacy Study of [redacted]
IMP Details	[redacted]

Protocol Reference	[redacted]
IRAS ID	[redacted]
Protocol Title	A Randomized, Open-label, Phase 3 Trial of [redacted]

IMP Details	[redacted]

Protocol Reference	[redacted]
IRAS ID	[redacted]
Protocol Title	A Phase 3, Randomized, Controlled, Open-Label, Clinical Study of [redacted]
IMP Details	[redacted]

Protocol Reference	[redacted]
IRAS ID	[redacted]
Protocol Title	A Randomized, Double-blind, Placebo-Controlled Phase 2 Study [redacted]
IMP Details	[redacted]

Protocol Reference	[redacted]
IRAS ID	[redacted]
Protocol Title	A Randomized Phase 3 Multicenter Open-label Study to [redacted]
IMP Details	[redacted]

Background Information

This was the fifth MHRA GCP systems inspection of Takeda Development Centre Europe Ltd (Takeda). The inspection was held remotely. The last MHRA GCP inspection was in June 2018.

[redacted]

Since the last inspection Takeda has acquired the following entities:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Starting in January 2020, Takeda Development Centres America (TDCA) is the legal entity/sponsor for new global clinical trials with some exceptions for vaccines trials (that are conducted under the legal entity of Takeda Vaccines Inc) and some legacy assets. In order to ensure business continuity for ongoing clinical trials, some regional legal entities were maintained and a notation that the regional legal entity is a “wholly owned subsidiary of Takeda” was added when protocol or ICF amendments were required for other reasons.

On 27 March 2023, Takeda migrated to a new Document Management System (DMS) and a new Learning Management System (LMS) on 27 March 2023 and 15 June 2023 respectively.

Definitions of Findings

Critical

a. Where evidence exists that significant and unjustified departure(s) from applicable legislative requirements has occurred with evidence that:

   i. the rights, safety or well-being of trial subjects either has been or has significant potential to be jeopardised, and/or

   ii. the clinical trial data are unreliable and/or

   iii. there are a number of Major non-compliances (defined in (d) and (e)) across areas of responsibility, indicating a systematic quality assurance failure, and/or

b. Where inappropriate, insufficient or untimely corrective action has taken place regarding previously reported Major non-compliances (defined in (d) and (e)).

c. Where provision of the Trial Master File (TMF) does not comply with Regulation 31A 1-3, as the TMF is not readily available or accessible, or the TMF is incomplete to such an extent that it cannot form the basis of inspection and therefore impedes or obstructs inspectors carrying out their duties in verifying compliance with the Regulations.

Major

d. A non-critical finding where evidence exists that a significant and unjustified departure from applicable legislative requirements has occurred that may not have developed into a critical issue, but may have the potential to do so unless addressed, and/or

e. Where evidence exists that a number of departures from applicable legislative requirements and/or established GCP guidelines have occurred within a single area of responsibility, indicating a systematic quality assurance failure.

Other

f. Where evidence exists that a departure from applicable legislative requirements and/or established GCP guidelines and/or procedural requirement and/or good clinical practice has occurred, but it is neither Critical nor Major.

Reference Texts

- UK Medicines Act 1968.
- The Human Medicines Regulations 2012, SI 1916 and the applicable statutory instruments including 2004/1031 (and subsequent amendments).
- ICH E6 “Note for Guidance on Good Clinical Practice”.
- Annex 13 to the EU Guide to Good Manufacturing Practice, ‘Manufacture of Investigational Medicinal Products’, July 2010.
- ICH E2A “Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting”.
- Communication from the Commission — Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the

notification of substantial amendments and the declaration of the end of the trial ('CT-1') (2010/C 82/01).

- Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') (2011/C 172/01).
- Heads of Medicines Agencies, Clinical Trial Facilitation & Coordination Group — Q&A Document: Reference Safety Information, November 2017 (RSI).

List of Common Abbreviations

AE	Adverse Event
ADR	Adverse Drug Reaction
ASR	Annual Safety Report
ATMP	Advanced Therapy Medicinal Product
CA	Competent Authority
CAPA	Corrective Action Preventive Action
CI	Chief Investigator
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CSR	Clinical Study Report
CSV	Computer Systems Validation
CTA	Clinical Trial Authorisation or Clinical Trial Agreement
CTFG	Clinical Trial Facilitation Group
CTIMP	Clinical Trial of an Investigational Medicinal Product
CV	Curriculum Vitae
DE	Dose Escalation
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
eCRF	Electronic CRF
eCOA	Electronic Clinical Outcome Assessment
ePRO	Electronic Patient Reported Outcome
eTMF	Electronic Trial Master File
FIH	First in Human
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HRA	Health Research Authority
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IRT	Interactive Response Technology
ISF	Investigator Site File/Investigator TMF
LPLV	Last Patient Last Visit
MAA	Marketing Authorisation Application
MHRA	Medicines and Healthcare products Regulatory Agency
MVR	Monitoring Visit Report
PI	Principal Investigator
PIS	Patient Information Sheet
PV	Pharmacovigilance
QA	Quality Assurance
QC	Quality Control
QMS	Quality Management System
QP	Qualified Person

RA	Regulatory Authority
R&D	Research and Development
REC	Research Ethics Committee
RMP	Risk Management Plan
RSI	Reference Safety Information
RWD	Real World Data
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SDR	Source Data Review
SmPC / SPC	Summary of Product Characteristics
SI	Sub-investigator
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TOPS	The Over-volunteering Prevention Scheme
UAT	User Acceptance Testing

Sponsor Inspection Findings

INSTRUCTIONS TO INSPECTED ORGANISATION

Inspection responses and any subsequent clarifications should be completed in the fields provided for each numbered finding. Please ensure there is a different row for each corrective and preventative action with the planned completion dates. Do not append any additional documentation or insert any file links. Please provide any other referenced documents as separate files.

No responses are required to any observations and recommendations.

1. Critical Findings

There was 1 **Critical finding** identified during this inspection relating to **Pharmacovigilance**.

1.1	**Pharmacovigilance** The rights, safety, and well-being of the trial subjects are the most important considerations and shall prevail over interests of science and society. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (1).** No person shall – (a) conduct a clinical trial; or (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. **UK Statutory Instrument 2004/1031 (as amended), Regulation 28 (1)** …Sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of good clinical practice are satisfied or adhered to. **UK Statutory Instrument 2004/1031 (as amended), Regulation 28 (2)** The necessary procedures to secure the quality of every aspect of the trial shall be complied with. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (4).** The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (8).** A sponsor shall ensure that all relevant information about a suspected unexpected serious adverse reaction (SUSAR) which occurs during the course of a clinical trial in the United Kingdom and is fatal or life-threatening is (a) recorded; and (b) reported as soon as possible to - … (i) the licensing authority… (iii) the relevant ethics committee, and in any event not later than 7 days after the sponsor was first aware of the reaction... **UK Statutory Instrument 2004/1031 (as amended), Regulation 33 (1)** A sponsor shall ensure that within 8 days of a report in accordance with paragraph (1)(b), any additional relevant information is sent to the persons or bodies listed in that paragraph. **UK Statutory Instrument 2004/1031 (as amended), Regulation 33 (2)** (3) A sponsor shall ensure that a suspected unexpected serious adverse reaction which occurs during the course of a clinical trial in the United Kingdom, other than those referred to in paragraph (1), is reported as soon as possible to - …. a) the licensing authority… (c) the relevant ethics committee, and in any event not later than 15 days after the sponsor is first aware of the reaction. **UK Statutory Instrument 2004/1031 (as amended), Regulation 33 (3)** A sponsor shall ensure that, in relation to each clinical trial in the United Kingdom for which he is the sponsor, the investigators responsible for the conduct of a trial are informed of any suspected unexpected serious adverse reaction which occurs in relation to an investigational medicinal product used in that trial, whether that reaction occurs during the course of that trial or another trial for which the sponsor is responsible. **UK Statutory Instrument 2004/1031 (as amended), Regulation 33 (5)** *58: The IB as last amended and approved by the national competent authority or equivalent document (e.g. SmPC for*

	marketed products) serves as the reference safety information for the assessment of the expectedness of any adverse reaction that might occur during the clinical trial. # **Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1), 2010/C 82/01** *55. The RSI may change during the conduct of a clinical trial. This is typically a substantial amendment (24). For the purpose of SUSAR reporting the version of the RSI at the moment of occurrence of the SUSAR applies (25). Thus, a change of the RSI impacts on the number of adverse reactions to be reported as SUSARs. Regarding the applicable RSI for the purpose of the annual safety report, see section 8* **Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') (2011/C172/01)** **Clinical Trial Facilitation Group (CTFG) 'Question and Answers: Reference Safety Information', November 2017**
	An impact assessment was provided to the MHRA as part of a Serious Breach notification (from June 2024) on the 14 August 2024 and again updated on 10 October 2024. On review of this impact assessment, it was noted that there were 15 under-reported SUSARs in relation to fatal and life-threatening events from Takeda between 01 November 2017 and 30 June 2024. As a result, this finding was graded as critical. Additional information is required to be provided in the response in relation to this impact assessment, dates the under-reported SUSARs were reported (and corresponding reference numbers), to include assessment of any fatal and life-threatening cases and the medical concept used. It was acknowledged that Takeda had completed the assessment on fatal and life-threatening cases against which version of the RSI was used. Specificity of the event should also be considered when assessing expectedness (in accordance with ICH E2A guidance in which reports which add to the specificity of an expected SAR should be considered unexpected (see also CTFG Q&A Questions 6 and 8).

Takeda Overarching Response to Critical Finding	
Evaluation & Root Cause	[redacted]

	[redacted]
Overarching Corrective Action 1	[redacted]

	[redacted]
Overarching Corrective Action 2	
Overarching Preventative Action 1	
Overarching Preventative Action 2	
Overarching Effectiveness Check	

1.1.1	Examples of incorrect expectedness assessment were identified during the inspection which resulted in incorrect information provided to the MHRA: • **Case** [redacted] described the life-threatening events of [redacted] (onset date [redacted] and [redacted] (onset date [redacted]): o This case was initially received by Takeda on 08 March 2019, followed by five significant follow-up reports. [redacted] IB version [redacted] that was effective at the events' onset date was used for the expectedness assessment for all the case versions. Life-threatening infections were not expected however the case was incorrectly assessed as expected in the initial version of the case due to oversight by the medical reviewer as per document request [redacted] It was acknowledged that the case was submitted to the MHRA within regulatory timelines (due to a SUSAR for other comparators), however, the reports incorrectly noted life-threatening [redacted] as expected for [redacted] as per IB version [redacted] • **Case** [redacted] described the life-threatening events of [redacted] and [redacted] (onset date [redacted]). o This case was initially received by Takeda on 05 June 2018, followed by two significant follow-up reports. [redacted] IB version [redacted] dated 26 October 2017 (Date RSI became effective: [redacted] that was effective at the event onset date was used for the expectedness assessment for all the case versions. Life-threatening [redacted] was not expected however the case was incorrectly assessed as expected in the initial version due to oversight by the medical reviewer as per document request [redacted] The expectedness assessment was not routinely re-evaluated in follow-up reports. Although all case versions of case [redacted] were submitted to MHRA as per the regulatory requirements (due to the event of [redacted] being correctly assessed as a SUSAR), the reports submitted to the MHRA incorrectly noted the event of life-threatening [redacted] as expected for [redacted] as per IB version [redacted]

Inspected Organisation's Response – 01 – 1.1.1	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 1.1.1	
	[redacted]
Overarching Corrective Action 1	[redacted]
Corrective Action 1	
Corrective Action 2	
Corrective Action 3	
Preventative Action 1	
Preventative Action 2	

Inspected Organisation's Response – 01 – 1.1.1	
	[redacted]
Preventative Action 3	
Preventative Action 4	
Effectiveness Check	
MHRA Review – 01 – 1.1.1	
[redacted]	
Inspected Organisation's Response – 02 – 1.1.1	
[redacted]	

MHRA Review – 02
Response accepted. It was assumed that the monthly quality checks conducted as part of Effectiveness check included all SUSARs, rather than those deemed Life threatening or fatal. If not, it is

MHRA Review – 02
expected that the 95% passing criteria is reviewed and amended to be more conservative.

1.1	Pharmacovigilance (continued)
1.1.2	Examples were identified during the inspection where the expectedness in the safety database's 'event assessment' tab was inadvertently updated upon receipt of non-significant follow-up information and displayed the incorrect expectedness assessment, leading to the changes of the initial report and subsequent incorrect listings. See examples below. • **Case** [redacted] initial and follow-ups (FU) 1-10) described an event of [redacted] (onset date [redacted] which was assessed as related to IMP [redacted] by the investigator. This event was assessed as expected despite all events being unexpected according to the RSI. It was explained in document request [redacted] that the event was assessed correctly by the medical review team as unlisted however, during a non-significant FU received by PV on 01 December 2022, the user inadvertently updated the expectedness assessment to listed. The case was not routed for medical review to assess the updates to the expectedness information as this was a non-significant FUP and the expectedness was updated in error. As this version of the case was processed as a non-significant update, there were no downgraded reports submitted to MHRA and therefore, no under-reporting. • **Case** [redacted] FU10) described a fatal/life-threatening event of [redacted](onset date [redacted] related to IMP [redacted] which was initially assessed correctly as unexpected by the medical reviewer. However, on 25 October 2022, during a non-significant update of the case, the expectedness of the event in 'event assessment' tab was inadvertently changed to expected. The reason why that change was performed was under investigation at the time of the inspection. The company comment section continued to mention the correct expectedness. Since this was a non-significant update, there was no submission to MHRA, and no SUSAR under-reporting. As this version of the case was processed as a non-significant update, there were no downgraded reports submitted to MHRA and therefore, no under-reporting. It was of note that non-significant follow-ups were not routed for medical review nor was the expectedness assessment routinely reviewed during follow ups as per document request [redacted]

Inspected Organisation's Response – 01 – 1.1.2	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 1.1.2	
	[redacted]
Overarching Corrective Action 1	
Corrective Action 1	
Corrective Action 2	
Preventative Action 1	
Preventative Action 2	
Preventative Action 3	
Effectiveness Check	

Inspected Organisation's Response – 01 – 1.1.2
[redacted]
MHRA Review – 01
Response accepted

1.1	Pharmacovigilance (continued)
1.1.3	The process to ensure that RSI updates were distributed to PV after receiving CA (MHRA) approval for implementation in case processing activities was inadequate or not followed. There were some examples identified of RSI updates that were not released to PV after MHRA approval. This could have resulted in incorrect reporting of SUSARs if expected events are added or removed from the updated RSIs. The PV team had not received the following IBs with updated RSIs from the [redacted] as required by [redacted] Version [redacted] Effective Date: 07 January 2024: • [redacted] IB version [redacted] dated [redacted] • [redacted] IB version [redacted] dated [redacted] • [redacted] IB version [redacted] dated [redacted] It was acknowledged that a quality event (QE) was raised with a date of awareness of 17 May 2024 following identification during inspection preparation activities that the PV team had not received the IBs. Takeda conducted an impact assessment prior to the inspection in June 2024 and no impact on safety was identified. However, these non-compliances were only identified as part of the inspection preparation and demonstrated that the CAPA since the previous inspection was ineffective. The previous inspection in 2018 identified a Major finding in relation to a lack of a robust process to ensure the RSI had been approved by the MHRA prior to implementation and use for the expectedness assessment of Serious Adverse Reactions.

Inspected Organisation's Response – 01- 1.1.3	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01- 1.1.3	
	[redacted]
Overarching Corrective Action 1	
Corrective Action 1	
Corrective Action 2	
Corrective Action 3	
Preventative Action 1	
Preventative Action 2	

Inspected Organisation's Response – 01- 1.1.3	
Effectiveness Check	[redacted]
MHRA Review – 01	
Response accepted	

1.1	Pharmacovigilance (continued)
1.1.4	Examples were identified during the inspection where unapproved RSIs were used to determine expectedness. [redacted] IB version [redacted] dated [redacted] was used to determine expectedness assessment prior to receiving MHRA approval on [redacted]. See examples below: **Case ID** / **Event Description** / **Onset Date(s)** [redacted] It was noted that this did not result in underreporting of SUSARs.

Inspected Organisation's Response – 01 – 1.1.4	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 1.1.4	
	[redacted]
Overarching Corrective Action 1	
Overarching Preventative Action 2	
Overarching Effectiveness Check	
Corrective Action 1	
Corrective Action 2	
Preventative Action 1	
Preventative Action 2	
MHRA Review – 01 – 1.1.4	
[redacted]	
Inspected Organisation's Response – 02 – 1.1.4	
[redacted]	

Inspected Organisation's Response – 01 – 1.1.4
[redacted]

MHRA Review – 02
Response accepted.

1.1	Pharmacovigilance (continued)
1.1.5	It was identified during the inspection that RSI was not being adequately controlled for non-Takeda products being used as IMPs (i.e. comparators): • The process for the regular review (e.g. determined by a risk assessment or at least annually) for any updates to the SmPC (used as an RSI for the comparator IMPs) was inadequate. Although the annual frequency was defined in the QMS [redacted] version [redacted] effective 07 January 2024) There was no instruction on how the review was conducted and documented (e.g. using the publicly available SmPC). • In addition, there was no requirement in the quality system to check if an update to a comparator SmPC had an impact on the PIS/ICF, protocol or overall risk benefit of the trial. It was explained during interview that only section 4.8 would be checked for updates to the RSI. *This was necessary not only to check for updates to the RSI, but in the case of an SmPC, there may have been changes to contraindications, warnings etc. that would have necessitated a protocol amendment in relation to inclusion or exclusion criteria. In addition, participants may have needed to be informed and consented if new safety information had come to light.* • There was also no evidence of oversight or compliance monitoring to ensure this activity was being performed.

Inspected Organisation's Response – 01 – 1.1.5	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 1.1.5	
	[redacted]
Overarching Corrective Action 1	
Overarching Preventative Action 2	
Overarching Effectiveness Check	
MHRA Review – 01	
Response accepted	

1.1	Pharmacovigilance (continued)
1.1.6	During the inspection, it was identified that the process for management of the RSI for non-Takeda comparators (when included in the SmPC) was not robust: • There were no procedural documents or process which detailed the requirement to implement comparator RSIs for SmPCs for expectedness assessment after regulatory authority approval, as this requirement was only stated for when the RSI was in the IB. [redacted] dated 19 August 2023 section 5.1 Notification of Implementation stated that '*GRL or delegate shall notify all relevant stakeholders (including* [redacted] *using* [redacted] *regarding substantial amendments to the IB due to RSI changes in programs with clinical trials (CTs) in countries requiring Health Authority approval before an updated RSI can be used for determination of expectedness (e.g., the EU/EEA and/or UK). The RSI can then be implemented for the assessment of expectedness of Suspected Serious Adverse Reactions'*. This may have led to the following examples identified during the inspection of comparators RSIs that were not submitted to the MHRA prior to being implemented for case expectedness assessments which included events that were unexpected in the MHRA approved RSI. See examples below (non-exhaustive):

	○ [redacted] ○ [redacted] ○ [redacted] It was confirmed in document request [redacted] that for comparators RSIs listed in document request [redacted] the 'date RSI became effective for Expectedness assessment in SAE case processing' reflected the 'internal protocol approval date', not the date of implementation. It was noted that deficiencies in the comparator RSI process which resulted in the use of unapproved RSIs for comparators were identified by Takeda on 23 May 2024, as part of the inspection preparation. Subsequently, a quality event [redacted] was opened to investigate this issue and an impact assessment was performed, which indicated that the use of the incorrect version of the RSI did not result in any under or over reporting of SUSARs, and therefore there was no impact on participant safety. However, it was identified as part of document request [redacted] that this impact assessment focussed on expectedness assessment (initial and follow-up) against the MHRA approved RSI at the time of SAE receipt, and did not include reviewing fatal / life threatening event expectedness, nor whether medical concepts were used to assess expectedness. • The RSI version used for expectedness assessments for comparator IMPs was not captured in the safety database or documented as described during interview. Therefore, it was not possible to re-construct which version of the comparator RSI was used for expectedness assessments by the Medical Reviewer or during case processing. • There was no procedural documentation to identify the RSI for a trial and to describe which exact section of the document was used to determine expectedness assessments, when the RSI was included in SmPC and/or USPI. For example: ○ For trial [redacted] the RSI for comparators [redacted] was not identified in the Regulatory Authority submission cover letters (initial and subsequent amendments) as required by CT-1. In addition, the RSI for comparators was also not mentioned in the protocol. ○ For trial [redacted] the RSI for comparators [redacted] was not identified in the Regulatory Authority submission cover letters as required by CT-1. In addition, the RSI for the above was also not mentioned in the latest version of the protocol.

Inspected Organisation's Response – 01 – 1.1.6	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 1.1.6	
	[redacted]
Overarching Corrective Action 1	
Overarching Preventative Action 2	
Overarching Effectiveness Check	
Corrective Action 1	
Preventative Action 1	
Effectiveness Check	
MHRA Review – 01	
Response accepted	

1.1	**Pharmacovigilance (continued)**
1.1.7	There was no procedural document which provided detailed instructions on how review of MedDRA updates (published every six months) to determine the impact on the RSI was conducted. In addition, it was not specified in the procedural documents that changes to the RSI due to MedDRA up-versioning would require a substantial amendment. As per [redacted] version [redacted] dated 12 August 2022, stated in relation to the RSI, '*The IB is reviewed annually based on the development international birth date (DIBD) or HA agreed international birth date and may be updated at other times with significant new information. The RSI should be reviewed only once per year, to coincide with the annual IB update and Annual Safety Report (ASR, such as the Development Safety Update Report [DSUR]*)'. However, this SOP did not detail how or how frequently the MedDRA updates review was conducted and documented, and the actions to be taken in case the MedDRA update had an impact on the RSI (i.e. change of PT requiring submission of a substantial amendment outside of the one-year period). It was acknowledged that evidence of impact assessment of 2022 and 2023 MedDRA updates on [redacted] IB were provided.

Inspected Organisation's Response – 01 -1.1.7	
Evaluation & Root Cause	[redacted]
Overarching Corrective Action 1	[redacted]
Overarching Preventative Action 2	
Overarching Effectiveness Check	
MHRA Review – 01	

Inspected Organisation's Response – 01 -1.1.7
Response accepted

1.1	Pharmacovigilance (continued)
1.1.8	There were inadequate procedural documents / processes to ensure that DSURs were managed adequately: • There was no process to ensure that the DSUR Cumulative Summary Tabulation of SAEs clearly identified SUSARs as required by ICH E2F and CTFG guidance. For example, the summary tabulations for the [redacted] DSURs (with the reporting periods of [redacted] did not clearly identify SUSARs and the DSUR appendix only provided a list of MedDRA PTs that were 'expected' in accordance with the latest version of the IB. • There was no process for ensuring that the DSUR listings were assessed against the RSI in effect at the start of the reporting period as per document request [redacted].As part of the response, Sponsor to provide outcome of impact assessment of DSURs and if any issues were identified. • An example was identified where multiple RSI versions were referenced in DSUR section 7.1 Reference Information: ○ [redacted] DSUR with a reporting period [redacted], section 7.1 stated that 'the IB edition [redacted] dated [redacted] and IB edition [redacted] dated [redacted] for [redacted] were used to determine expectedness for the events presented in Appendix R1 [Cumulative Summary Tabulations of Serious Adverse Reactions]'. This was incorrect as only the RSI version in effect at the start of the reporting period should have been used. As part of the response, Sponsor to provide outcome of impact assessment of DSURs and if any issues were identified.

Inspected Organisation's Response – 01 – 1.1.8	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 1.1.8	
	[redacted]
Overarching Corrective Action 1	
Overarching Preventative Action 2	
Preventative Action 1	
Preventative Action 2	
Preventative Action 3	
Preventative Action 4	

Inspected Organisation's Response – 01 – 1.1.8	
	[redacted]
Effectiveness Check 1	
Effectiveness Check 2	

Inspected Organisation's Response – 01 – 1.1.8	
	[redacted]
MHRA Review – 01	
Response accepted	

1.1	Pharmacovigilance (continued)
1.1.9	There was no contemporaneous documentation, either in the case folder within the safety database itself or in other supporting documentation, of the RSI version used to assess the expectedness for comparators when the RSI was contained in SmPCs. It was not possible to determine which version of the RSI was used to assess expectedness of initial cases or determine that the same RSI was used consistently for follow-up cases.

Inspected Organisation's Response – 01 – 1.1.9	
Evaluation & Root Cause	[redacted]
Overarching Corrective Action 1	
Overarching Preventative Action 2	

Inspected Organisation's Response – 01 – 1.1.9	
Overarching Effectiveness Check	[redacted]
MHRA Review – 01	
Response accepted	

2. Major Findings

There were **5 Major findings** identified during this inspection relating to **Quality Systems**, **Serious Breach Reporting**, **Training, Project / Trial Management** and **Pharmacovigilance**.

2.1	**Quality Systems** No person shall – (a) conduct a clinical trial; or (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. **UK Statutory Instrument 2004/1031 (as amended), Regulation 28 (1)** …Sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of good clinical practice are satisfied or adhered to. **UK Statutory Instrument 2004/1031 (as amended), Regulation 28 (2)** The necessary procedures to secure the quality of every aspect of the trial shall be complied with. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (4).**
2.1.1	During the inspection, there were a number of 'business processes' described in interview sessions as used routinely for a number of procedures. However, these were not formalised processes. See examples below (list not exhaustive): **Risk Based Assessments** • A risk-based approach was described as being used by Takeda Learning Partners (LP) to assess training requirements. A Risk Based Assessment checklist was used for this assessment but was not a formalised procedure or document. See finding 2.3.1 for more details. • Risk-based assessments did not specifically include vendor risk assessment details. **Protocol Amendment Impact Assessments** • There was no formalised document or tool used to document the impact assessment for an amendment to a protocol or IB. A business process template

	was used to capture the key changes and impact. See finding 2.4.3. • There was no formalised procedure to confirm or document any impact assessments of protocol amendments in relation to training documentation and assessments. However, a business process template was routinely used. See finding 2.3.1 for more detail. • There was no formalised or documented process for the release of system updates in alignment with UK approvals of protocol amendments despite the process being described as a 'business process'. Therefore, due to the systemic deficiency in the formalisation of the Quality Management System, it was unable to be verified that processes carried out were consistent throughout.

Inspected Organisation's Response – 01 – 2.1.1	
Evaluation & Root Cause	[redacted]
Corrective Action	

Inspected Organisation's Response – 01 – 2.1.1	
Preventative Action 1	[redacted]
Preventative Action 2	
Preventative Action 3	
Preventative Action 4	
Effectiveness Check 1	
Effectiveness Check 2	
Effectiveness Check (PA4)	
MHRA Review – 01	
Response accepted	

2.1	Quality Systems (continued)

2.1.2	There was a lack of formalised procedures for trial management during the time the trials in scope were conducted: • There was no formalised procedure which outlined the requirement for retention of eSystems training (or User Access Logs where this was linked to access). • There was no formalised procedure within the QMS which defined which plans needed to be put in place until June 2024. Of note, it was highlighted in document request [redacted] under the 'Responsibility for Oversight of the Execution' of the Data Access Management Plan (DAMP) this was listed as not applicable. • There was no formalised requirement to document assessment and impact of protocol amendments to the Electronic Data Capture Systems (EDC).

Inspected Organisation's Response – 01 – 2.1.2	
Evaluation & Root Cause	[redacted]
Corrective Action	
Preventative Action 1	
Preventative Action 2	
Preventative	

Inspected Organisation's Response – 01 – 2.1.2	
Action 3	[redacted]
Effectiveness Check 1	
Effectiveness Check 2	
Effectiveness Check 3	
MHRA Review – 01	
Response accepted	

2.2	**Serious Breach Reporting** (1) The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of (a) the conditions and principles of good clinical practice in connection with that trial; or (b) the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25, within 7 days of becoming aware of that breach. (2) For the purposes of this regulation, a "serious breach" is a breach which is likely to effect to a significant degree (a) the safety or physical or mental integrity of the subjects of the trial; or (b) the scientific value of the trial. **UK Statutory Instrument 2004/1031 (as amended), Regulation 29A** The necessary procedures to secure the quality of every aspect of the trial shall be complied with. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (4).**
2.2.1	The process for management of potential serious breaches was inconsistent and not sufficiently robust: A) It was identified during the inspection that Takeda would only report once a serious breach was confirmed, which could be some time after Takeda (or delegated service provider) became aware of a potential serious breach. Therefore, there was a risk of non-adherence to the legislative requirements to report within 7 days because of the lengthy durations of investigations. For example, of the 8 Serious Breach reports made to MHRA since 2018 in relation to trials sponsored by Takeda (or other sponsors within the Takeda organisation), 4 were reported beyond the 7-day legislative requirement based on the date of awareness, rather than date of determination: Takeda Serious Breach/Scientific Misconduct Numbers [redacted] that were reported at 10, 14, 74 and 38 days after date of

	awareness respectively. B) There was no process to consider the potential impact and determine if reporting to the MHRA, pending further investigation, would be appropriate. C) The QMS was inconsistent on the definition of day 0. SOP [redacted] dated 16 December 2022 indicated within the same document the following: o Day 0 was the date in which Takeda or a delegated party responsible for Serious GCP Breach assessment and/or reporting (i.e., CRO) become aware of a serious GCP breach or scientific misconduct or significant GxP noncompliance. o Day 0 was the date of awareness 0 in which Takeda or delegated party was first informed/received information that provides reasonable grounds to believe that a serious breach had occurred. Although the inconsistency between the SOP and QMS had been acknowledged, Inspectors were informed that Takeda believe Day 0 to be the date of determination.

Inspected Organisation's Response – 01 – 2.2.1	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 2.2.1	
	[redacted]
Corrective Action	
Preventative Action 1	

Inspected Organisation's Response – 01 – 2.2.1	
Preventative Action 2	[redacted]
Effectiveness Check	
MHRA Review – 01	
Response accepted	

2.2	Serious Breach Reporting (continued)
2.2.2	The impact assessments for RSI issues identified in preparation for the inspection were not reported as a Serious Breach. It was explained during interview that this was because the investigation revealed there were no under-reported SUSARs. On inspection, it was identified that this investigation and impact assessment was not comprehensive and required further review. This review had led to the discovery of a multiple missed SUSARs to the MHRA. See Finding 1.1 for more information.

Inspected Organisation's Response – 01 – 2.2.2	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 2.2.2	
	[redacted]
Corrective Action	
Preventative Action	
Effectiveness Check	
MHRA Review – 01	

Inspected Organisation's Response – 01 – 2.2.2
Response accepted

2.3	**Training** The rights, safety and well-being of the trial subjects shall prevail over the interests of science and society **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (1).** No person shall – (a) conduct a clinical trial; or (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. **UK Statutory Instrument 2004/1031 (as amended), Regulation 28 (1)** …Sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of good clinical practice are satisfied or adhered to. **UK Statutory Instrument 2004/1031 (as amended), Regulation 28 (2)** Each individual involved in conducting a clinical trial shall be qualified by education, training and experience to perform his tasks. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (2).** The necessary procedures to secure the quality of every aspect of the trial shall be complied with. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (4).** The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (8).**
2.3.1	Formalised processes in relation to training were not adequate: A) The risk based approach undertaken by Takeda Learning Partners (LP) in assessing the training requirements of a new process was not formalised: • A 'Learning Partner' Checklist was described as being routinely used by the LPs to make this assessment, yet this was described as a business process which was not formalised. As a result, there was no requirement for the checklist to be used even though this was integral in determining how training should be developed and disseminated. • There was no formalised approach to documenting risk assessments in relation to assessing the suitability of training methodology. It was noted that [redacted] effective 07 November 2023 stated a Training Risk Based Approach (RBA) evaluation was used, however there was no formalised process to complete the assessment or capture the outcome. B) It was identified during the inspection, that although line managers were required to periodically review that employees had undertaken the required training, this review period was not defined within the QMS; [redacted] dated 09 August 2021, stated that *'Personnel / workers training assignments / curricula / learning plan shall be assessed periodically'*, however, there was no definition of the review period. C) It was described during interview that line managers were required to check that training on clinical trials SOPs had been performed prior to undertaking the activity but this requirement was not stipulated in the QMS. D) Until March 2024 (after the dossier request had been sent to Takeda on 06 February 2024) there was no requirement in the QMS to define and document

	the training requirements for a clinical trial (e.g. training matrix). E) There was no formalised procedure to confirm or document any impact assessments conducted due to protocol amendments. It was noted that current procedures to assess changes are formalised in the [redacted] effective date 01 April 2024. However, there was no formalised document or tool used to capture the change, there was a 'business process template' which was not routinely used.

Inspected Organisation's Response – 01 – 2.3.1	
Evaluation & Root Cause	[redacted]
Corrective Action	
Preventative Action 1	
Preventative Action 2	

Inspected Organisation's Response – 01 – 2.3.1	
	[redacted]
Preventative Action 3	
Preventative Action 4	
Effectiveness Check 1	
Effectiveness Check 2	
Effectiveness Check 3	

MHRA Review – 01 – 2.3.1
[redacted]

Inspected Organisation's Response – 02 – 2.3.1
[redacted]

MHRA Review – 02
Response accepted. It is expected that formal processes such as SOPs reflect the information presented in the CAPA and Inspected Organisation's Response.

2.3	Training (continued)
2.3.2	Formalised processes in relation to Takeda oversight of training were not adequate: A) Prior to April 2024, there was no formalised process which outlined requirements or mandated any documentation of trial-specific training by CRAs. As a result of this, there was no evidence of Takeda oversight of trial-specific training or tracking of training for any of the trials in scope. This had been reviewed by Takeda as part of an undergoing transformation and review of SOPs, and a new Study Training Matrix was made effective in April 2024. B) There was no formalised process or evidence of document approval and therefore adequate oversight by Takeda of training material that had been co-developed by external parties. Therefore, documentation of Takeda's oversight of training materials development, approval and delivery was not available. Examples were seen in document request [redacted] where, even though it was indicated as 'Yes' in the column for evidence of oversight for approval of training or having Takeda review and approval, when asked for evidence of this no documentation of oversight was available in the links provided. See examples for the trials below: ○ [redacted] dated 11 October 2019. ○ [redacted] Site Initiation Visit (SIV) dated 17 September 2012 and Investigator Meeting dated 19 October 2017. C) There were no formalised procedures / documents that defined the requirements of who was responsible for generating trial-specific training. Although it was described in some Master Service Agreements that parties would work together to determine training requirements, there was no formalised procedures to specify creators of training documentation or documentation to evidence Takeda oversight / approval of training materials.

Inspected Organisation's Response – 01 – 2.3.2	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 2.3.2	
	[redacted]
Corrective Action	
Preventative Action 1	
Preventative Action 2	
Effectiveness Check	
MHRA Review – 01	
Response accepted.	

2.3	Training (continued)
2.3.3	It was described to inspectors during interview that the risk-based process for determining the method of training was not used for GCP Training. Although, it was determined that an eLearning be developed to enhance the delivery of content, there was no documented evidence to support the approach of utilising an eLearning format (as decided in June

	2022). It was noted that SOP [redacted] effective date 07 November 2023, did mention the following as the responsible role for the Regulated Training materials owner *'Selects the delivery method(s) needed per identified impacted training audience (considering access to technology e.g.: computer access, classrooms, working environment' and* *'Uses a Training Risk Based Approach (RBA) evaluation, so regulated training materials may require a means of assessing learning and retention to determine if the learning objectives have been met.* *This is accomplished via a learning assessment, which can take the form of a demonstration, trainer/trainee discussion, Q&A session, quiz or exam, or other means as determined by the Training Function, regulated training materials Author, or Business Process Owner.* *Ensures training methodology and assessment requirements are determined based on criticality, complexity and frequency of execution of the task.'*

Inspected Organisation's Response – 01 – 2.3.3	
Evaluation & Root Cause	[redacted]
Corrective Action	
Preventative Action	
Effectiveness Check	
MHRA Review – 01	
Response accepted	

2.3	**Training (Continued)**

2.3.4	It was described to inspectors during interview that the documentation of training records held in the eTMF were inconsistent, including CRA training or system dependent training (such as eCRF training). Therefore, the eTMF did not contain contemporaneous and accurate training records. It was described, if a new CRA were to start on a trial at a CRO, Takeda would rely on the CRO to maintain copies of Takeda trial-specific training. An example was identified that Takeda was unable to provide the training record for CRA [redacted] completing [redacted] dated 23 February 2017.

Inspected Organisation's Response – 01 – 2.3.4	
Evaluation & Root Cause	[redacted]
Corrective Action	
Preventative Action 1	
Preventative Action 2	
Effectiveness Check 1	
Effectiveness Check 2	
MHRA Review – 01 – 2.3.4	
[redacted]	
Inspected Organisation's Response – 02 – 2.3.4.	
[redacted]	

Inspected Organisation's Response – 01 – 2.3.4
[redacted]

MHRA Review – 02
Response accepted.

2.4	**Project / Trial Management** The rights, safety and well-being of the trial subjects shall prevail over the interests of science and society **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (1).** No person shall – (a) conduct a clinical trial; or (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. **UK Statutory Instrument 2004/1031 (as amended), Regulation 28 (1)** …Sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of good clinical practice are satisfied or adhered to. **UK Statutory Instrument 2004:1031 (as amended), Regulation 28 (2)** The necessary procedures to secure the quality of every aspect of the trial shall be complied with. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (4).** The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (8).**
2.4.1	Examples were identified of various trial-specific plans not being in place prior to study start up. For the [redacted] trial, the first site activated was on 31 March 2023, however the following plans were in place after this: **Document Name** / **Document Date** [redacted] / 13 October 2023 [redacted] / 24 January 2024 [redacted] / 24 January 2024 It was noted that required timelines were set out in [redacted] approved 19 June 2023, which was after the

	first site had been activated for this trial in which it stated *'The IQRMP and CMP are to be finalized by First Site Activated (FSA) and reviewed and approved prior to initiating activities defined in the plan taking place'.* The CMP in this case referred to the 'Centralized Data Monitoring Plan'.

Inspected Organisation's Response – 01 – 2.4.1	
Evaluation & Root Cause	[redacted]
Corrective Action	
Preventative Action	
Effectiveness Check	
MHRA Review – 01	
Response accepted	

2.4	**Project / Trial Management (continued)**
2.4.2	Implementation of protocol amendments at investigator sites was not robust: • The implementation of protocol amendments by [redacted] for the [redacted] trial did not require (in the Investigator Agreement section) ensuring that the PI had signed the new protocol despite wording which affirmed PI conduct in the trial in line with regulations and GCP Principles. This was evident for all sites and all amendments implemented at UK sites. • Takeda had no process to ensure that electronic systems were consistent with the protocol approved by the MHRA, REC, HRA and site approvals as there was no ability to release systems at country or site level. For the [redacted] trial, this lack of oversight by Takeda and their delegated CRO meant that the eCRF [redacted] which was associated with protocol

	amendment [redacted] was released into production on [redacted] and available for UK sites prior to MHRA, REC and HRA approvals ([redacted] respectively). It was evidenced in the audit trail that the unapproved protocol was initially selected (for site [redacted] and required to be changed, but this illustrated the risk, that if it had not been identified, this may have caused changes in forms or dynamic flows within the eCRF which may have led to non-compliance or data integrity issues. Of note, if this had happened in an eSystem where critical functionality occurs, such as dosing calculations, this could lead to trial participant harm. • For the [redacted] trial, database modification (DB) [redacted] in relation to the EDC [redacted] and Protocol Amendment (PA) [redacted] and had a go live date of [redacted] This was prior to CA approval ([redacted] . There were 2 active participants at site [redacted] at this time. [redacted] was implemented at this site on [redacted], therefore, this EDC was available prior to site implementation. It was described to inspectors that sites were advised not to use [redacted], there was the risk that the new updated EDC would have been available to them during this time period. • For the [redacted] dated 21 April 2020 was given a grounds for non-acceptance by the MHRA but this was still deployed at a protocol level in the EDC. DB Modification [redacted] was released to UK sites, despite this not being approved by the MHRA. It was noted, however, that this update occurred after the final UK subject had exited the study. **As part of the response, Takeda is required to assess if the DB modification altered any existing data within the EDC, and if this subsequently affected data integrity or management processes for this particular trial.**

Inspected Organisation's Response – 01 – 2.4.2	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 2.4.2	
	[redacted]
Corrective Action 1	
Corrective Action 2	
Corrective Action 3	
Preventative Action	
Effectiveness Check	
MHRA Review – 01	
Response accepted	

2.4	Project / Trial Management (continued)
2.4.3	There was no formalised process / tool to document the impact assessment for an amendment to a protocol or IB. It was noted that that there was a business process template that captured the key changes, the operational update(s) required and the impact of the change but this was not formalised.

Inspected Organisation's Response – 01 – 2.4.3	
Evaluation & Root Cause	[redacted]
Corrective Action	
Preventative Action	
Effectiveness Check	
MHRA Review – 01 – 2.4.3	
[redacted]	
Inspected Organisation's Response – 02 – 2.4.3	
[redacted]	

Inspected Organisation's Response – 01 – 2.4.3
[redacted]

MHRA Review – 02
Response accepted.

2.4	Project / Trial Management (continued)
2.4.4	It was identified as part of document request [redacted] that risk assessments for the [redacted] trial were not completed in a timely manner. The FPFV globally was on [redacted] and in the UK this was [redacted]. However, the first trial risk assessments were implemented in [redacted] 2 years after the trial had started.

Inspected Organisation's Response – 01 – 2.4.4	
Evaluation & Root Cause	[redacted]
Corrective Action	
Preventative Action 1	

Inspected Organisation's Response – 01 – 2.4.4	
Preventative Action 2	[redacted]
Effectiveness Check	
MHRA Review – 01	
Response accepted	

2.4	Project / Trial Management (continued)
2.4.5	Examples were identified where documentation of which SOPs and Templates were used by the CRO or Takeda for specific trials were not consistently documented. The database lock and unlock processes, monitoring activities and eSystem validation activities for the [redacted] trial used the CRO templates, however, this was not documented within Takeda documentation.

Inspected Organisation's Response – 01 – 2.4.5	
Evaluation & Root Cause	[redacted]
Corrective Action	
Preventative	

Inspected Organisation's Response – 01 – 2.4.5	
Action	[redacted]
Effectiveness Check	
MHRA Review – 01 – 2.4.5	
[redacted]	
Inspected Organisation's Response – 02 – 2.4.5	
[redacted]	

MHRA Review – 02
Response accepted.

2.4	Project / Trial Management (continued)
2.4.6	Oversight activities were not defined in a trial-specific plan. It was noted that there was a general SOP which covered this, [redacted]

Inspected Organisation's Response – 01 – 2.4.6	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 2.4.6	
	[redacted]
Corrective Action	
Preventative Action	
Effectiveness Check	
MHRA Review – 01 – 2.4.6	
[redacted]	
Inspected Organisation's Response – 02 – 2.4.6	
[redacted]	

MHRA Review – 02
Response accepted.

2.5	**Pharmacovigilance** The rights, safety, and well-being of the trial subjects are the most important considerations and shall prevail over interests of science and society.

	UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (1). No person shall – (a) conduct a clinical trial; or (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. **UK Statutory Instrument 2004/1031 (as amended), Regulation 28 (1)** …Sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of good clinical practice are satisfied or adhered to. **UK Statutory Instrument 2004/1031 (as amended), Regulation 28 (2)** The necessary procedures to secure the quality of every aspect of the trial shall be complied with. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (4).** A sponsor shall ensure that all relevant information about a suspected unexpected serious adverse reaction (SUSAR) which occurs during the course of a clinical trial in the United Kingdom and is fatal or life-threatening is (a) recorded; and (b) reported as soon as possible to - … (i) the licensing authority… (iii) the relevant ethics committee, and in any event not later than 7 days after the sponsor was first aware of the reaction... **UK Statutory Instrument 2004/1031 (as amended), Regulation 33 (1)** A sponsor shall ensure that, in relation to each clinical trial in the United Kingdom for which he is the sponsor, the investigators responsible for the conduct of a trial are informed of any suspected unexpected serious adverse reaction which occurs in relation to an investigational medicinal product used in that trial, whether that reaction occurs during the course of that trial or another trial for which the sponsor is responsible. **UK Statutory Instrument 2004/1031 (as amended), Regulation 33 (5)**
2.5.1	There was a lack of a robust process to ensure pregnancy reports had been followed up appropriately and all efforts have been made by Takeda to obtain information on outcomes from investigator sites. During interview, the process described relied upon responses from service providers to close queries in the safety database. However, responses were not required from an investigator to complete this. It was also confirmed during interview that no reconciliation was completed between the safety database and EDC on pregnancy reports and outstanding queries. There was a risk that there was a lack of follow-up to obtain this exposure data and whether any potential SAEs may be missed following outcomes for downstream reporting of safety information in clinical study reports, DSURs and SUSARs as applicable. The lack of robust processes included: • Lack of follow-up of pregnancy outcomes for participants as identified in interview and document request [redacted] • Examples were identified in which pregnancy follow-up queries could not be located in EDC or the safety database: o For Cases [redacted] there was no evidence available relating to queries as detailed in document request [redacted] and request [redacted] o For [redacted] Takeda could not locate any further documentation besides the pregnancy notification. It was noted that there was a request for the site to follow-up with the pregnancy until final outcome, but no further documentation was provided. o For case [redacted] the event outcome and foetal outcome were received from the site on [redacted] Although the event outcome and stop date were captured in [redacted] during processing of the follow-up, the foetal outcome

was not entered in the correct structured fields. This was explained by Takeda was human error during data entry.

- When follow-up queries were actioned, this was not always consistent as per document request [redacted]
    - For Case [redacted], a follow-up query was not prompted to the clinical site to collect the pregnancy outcomes, after Takeda was aware from processing the initial information on [redacted] It was noted however, that the site themselves provided pregnancy statuses and delivery information.
- Lack of follow-up of pregnancy outcomes for pregnant partners of participants which may have resulted in the below:
- Lack of follow-up of informed consent to obtain information on outcomes for pregnant partners of participants
- Procedures for follow-up of pregnancies was not robust.

  For example, [redacted] dated 29 March 2024 required 3 follow-up attempts to be made on a pregnancy report and an attempt to be made 30 days post estimated delivery date. If this was not received at this attempt then the pregnancy outcome should have been reported as 'unknown'.
  There was no link to other mechanisms to follow-up or reference to database locks or important milestones such as development of the DSUR to ensure the outcome information was obtained. For example, a link to database lock, CSR, study closure and for those whose outcomes would be known after the DBL date.
- Pregnancy cases were not closed in the database prior to notification of the inspection. E.g. Document Request [redacted] showed the following cases were not closed in the database and these were subsequently closed by Takeda in the safety database; [redacted]

As part of the response to this report, Takeda was requested to assess all the cases that had not been appropriately followed up including up to pregnancy outcome and further if required by protocol, provide reasoning and the potential impact of this (including any missed SAEs) for trial participants and partners.

For the cases with no outcome (not reported / lack of follow-up / request for consents to obtain information on outcomes (pregnant partners for male participants), i.e. when the outcome was unknown, Sponsor was to clarify how it could be ensured that all efforts had been made by Takeda to obtain information on outcomes from investigator sites.

Takeda was also required to assess the impact in relation to the reconciliation between the safety database and the EDC.

Takeda was requested to reconcile all pregnancy cases within the safety database with the EDC in particular in relation to pregnancy reports and outstanding queries. (to ensure data matches).

Inspected Organisation's Response – 01 – 2.5.1	
Evaluation & Root Cause	[redacted]
Corrective Action 1	
Corrective Action 2	
Corrective Action 3	
Corrective	

Inspected Organisation's Response – 01 – 2.5.1	
Action 4	[redacted]
Preventative Action 1	
Preventative Action 2	
Preventative Action 3	
Effectiveness Check	
MHRA Review – 01 – 2.5.1	
[redacted]	

Inspected Organisation's Response – 01 – 2.5.1
Inspected Organisation's Response – 02 – 2.5.1
[redacted]

MHRA Review – 02
Response accepted.

3. Other Findings

There were **5 Other findings** identified during this inspection relating to **False and Misleading**, **Quality Assurance**, **IMP Management / Pharmacy**, **Record Keeping / Essential Documents** and **Sponsor Oversight of CTIMPs**.

3.1	**False and Misleading**
3.1.1	During the inspection, it was identified that information provided to the inspectors included missing or incorrect information despite having been informed these had undergone QC processes. See examples below (list not exhaustive): A) The MHRA approval date for [redacted] IB Edition [redacted] dated [redacted] was reported in document request [redacted] as [redacted], however, the MHRA approval date was on [redacted] and was subsequently confirmed by Takeda that this was an error. B) The list of RSI versions and summary of changes provided in response to document request [redacted] contained significant errors. For example, [redacted] IB Edition [redacted] was not included. C) [redacted] Ed [redacted] included [redacted] as an expected event but this was not listed in [redacted] therefore significant time was spent investigating potential cases of unreported SUSARs. D) The memo provided with [redacted] and [redacted] stated *'for* [redacted] *certain data elements such as submission information and event assessment for period 2013 - 2015 have been requested from* [redacted] *Takeda reported all the information available within the Takeda safety database including ICSRs received prior to 19-Jan-2015 for IMP* [redacted] *while waiting for information from our partner. Takeda intends to submit any subsequent information received from its partner as an addendum to the original response.'* This was because at that time, [redacted] was responsible for event assessment and submission, and Takeda was receiving CIOMS reports. However, upon receipt of the updated listings [redacted] it was identified that the missing

	data also impacted cases (follow-ups) received after 2015 and [redacted] cases (comparator arm of the [redacted] trial). E) The change control spreadsheet for the [redacted] trial had the incorrect protocol implementation dates entered. F) The GCP Inspection Dossier Clinical Trial Spreadsheet contained incorrect information: • In document request [redacted] he FPFV was correctly listed as [redacted] however, in the Clinical Trial Spreadsheet provided as part of the dossier incorrectly reported the date of [redacted] which was the first participant randomised globally. • For trial [redacted] the UK trial start date was [redacted] however the Clinical Trial Spreadsheet incorrectly reported the date as [redacted] which was the first participant randomised globally. As a result, SAEs were requested from 2016 needlessly. • As part of the inspection, Takeda was requested to provide a list of trial-specific training, with information of who had developed the training with evidence of Takeda oversight. As part of document request [redacted] and subsequent follow-ups and QC checks, it was evident that the TMF links provided did not always document evidence of Takeda's review and approval and was acknowledged that this was not consistently documented. G) Document request [redacted] had two parts, yet the response memo and documentation provided only covered the first part of the request. A follow-up was then required to obtain the information originally requested adding unnecessary delays in the inspection process and demonstrating a lack of QC to ensure the information provided to inspectors was accurate.

Inspected Organisation's Response – 01 – 3.1.1	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 3.1.1	
	[redacted]
Corrective Action	
Preventative Action 1	
Preventative Action 2	
MHRA Review – 01	
Response accepted	

3.1	False and Misleading (continued)
3.1.2	The list of IMP orders, shipment, receipt and acknowledgement dates from the [redacted] IRT system as detailed in document request [redacted] was incorrect. See below for examples identified in which shipment dates had been documented incorrectly: • Shipment [redacted] to site [redacted] had a delivery date of 17 October 2014, prior to the shipment date of 20 October 2024. It was confirmed in document request [redacted] that the correct shipment date was 16 October 2014 and order was delivered on 17 October 2024.

	• Shipment [redacted] to site [redacted] had a shipment date of 09 December 2015, however actual shipment date was 08 December 2015. The error was due to staff at [redacted] warehouse staff not capturing the revised dispatch date in the [redacted] system which was subsequently imported into the study's IRT system. Therefore, the IRT system contained errors and this had not been identified through oversight mechanisms ahead of the inspection. **As part of the response, Takeda to review shipment dates for incorrect dates, and investigate if these errors are across other trials.**

Inspected Organisation's Response – 01 – 3.1.2	
Evaluation & Root Cause	[redacted]
Corrective Action	
Preventative Action	
MHRA Review – 01	
Response accepted	

3.2	Quality Assurance
3.2.1	Examples were identified during this inspection of inadequate control and use of RSI. Related QEs ([redacted] raised by Takeda in preparation for this inspection, were repeated findings from the last GCP inspection. This demonstrated inadequate and ineffective CAPA. See finding 1.1.3 for more information.

Inspected Organisation's Response – 01 – 3.2.1	
Evaluation & Root Cause	[redacted]
Corrective Action	
Overarching Preventative Action 2	
Overarching Effectiveness Check	
MHRA Review – 01	
Response accepted	

3.2	Quality Assurance (continued)

3.2.2	The impact assessment conducted in 2018 and 2019 after the previous MHRA GCP inspection only focused on expectedness assessments (initial and follow-up) against the MHRA approved RSI at the time of occurrence, i.e. onset date. The CTFG guidance published in November 2017 was used to guide these assessments, however, it was not a comprehensive review as it did not include reviewing fatal life-threatening event expectedness, nor whether medical concepts were used to assess expectedness. Following the 2018 GCP PV impact assessment, Takeda was required to conduct an impact assessment to identify whether the deficiencies identified led to under or late reporting of SUSARs, in line with the CTFG guidance to guide the assessment. Although the impact assessment report for the 2018 GCP PV impact assessment was submitted to the MHRA prior to the issuance of the final inspection report issued on 14 August 2018, it was Takeda's responsibility to ensure that the methodology used was in line with the MHRA expectations.

Inspected Organisation's Response – 01 – 3.2.2	
Evaluation & Root Cause	[redacted]
Corrective Action 1	
Corrective Action 2	

Inspected Organisation's Response – 01 – 3.2.2	
	[redacted]
Corrective Action 3	
Corrective Action 4	
Preventative Action 1	
Preventative Action 2	
Effectiveness Check	
MHRA Review – 01	
Response accepted	

3.3	**IMP Management / Pharmacy**
3.3.1	[redacted] QP technical release was performed prior to receiving MHRA approval for the trial. QP technical release was performed by [redacted] on [redacted], prior to the MHRA CTA notice of acceptance of amended request dated [redacted] which approved the trial subject to conditions. It was noted, that QP release was issued for each batch of IMP, but that Individual countries were not listed on the [redacted] QP documentation. Therefore, it was not possible to confirm how the QP could release the product in accordance with article 13.3 of Directive 2001/20/EC as stated on the certificate. **As part of the response, Takeda to clarify if IMP undergoes a separate 'Regulatory Release' of IMP, and assess if this release was prior to MHRA Regulatory Approval.**

Inspected Organisation's Response – 01 – 3.3.1	
Evaluation & Root Cause	[redacted]
Corrective Action	
Preventative Action	
Effectiveness Check	

Inspected Organisation's Response – 01 – 3.3.1
MHRA Review – 01 – 3.3.1
[redacted]
Inspected Organisation's Response – 02 – 3.3.1
[redacted]

MHRA Review – 02
Response accepted.

3.4	**Record Keeping / Essential Documents**
3.4.1	A) A number of examples were identified of documents missing or not filed in the eTMF for the [redacted] trial, despite this trial being completed (final CSR dated [redacted] : • [redacted] EDC database specifications for the following database modifications: o Modification [redacted], updated field name in eCRF and edit check updates, go live date [redacted] o Modification [redacted], CRF enhancements and edit check updates, go live date [redacted] It was noted that none of the above changes were related to a protocol amendment as per document request [redacted] • Evidence of QP Technical release for the UK was not in the eTMF. Document request [redacted] confirmed that it was misfiled in a secondary filing location due to a miscommunication. It was recommended to Takeda that an assessment of secondary filing locations and the completeness of the [redacted] eTMF was required before archiving. B) It was noted that as per response to document request [redacted] Takeda confirmed that they currently do not have a procedure associated with the retention of records pertaining to eSystems training and user access logs but were working on developing procedures. C) It was also confirmed that Takeda do not retain records for training performed by

		service provider staff, only site training records in the eTMF. Therefore, evidence of CRO staff training on systems and when this was completed was not available in the TMF. See finding 3.5.1.

Inspected Organisation's Response – 01 – 3.4.1	
Evaluation & Root Cause	[redacted]
Corrective Action 1	
Corrective Action 2	
Corrective Action 3	
Corrective Action 4	
Preventative	

Inspected Organisation's Response – 01 – 3.4.1	
Action 1	[redacted]
Preventative Action 2	
Preventative Action 3	
Preventative Action 4	
Effectiveness Check 1	
Effectiveness Check 2	
Effectiveness Check 3	
MHRA Review – 01	
Response accepted	

3.5	**Sponsor Oversight of CTIMPs**
3.5.1	There was no requirement in the QMS for Takeda to oversee that trial-specific training had been undertaken for activities delegated to a service provider. Takeda was reliant on the CRO overseeing that training had been performed by all relevant roles, functions and sites, and did not have a requirement independent of the CRO. During interview, it was described that trial-specific training undertaken by CRAs would be filed in the CRO's LMS and not filed in the eTMF. There was no mechanism for Takeda to have oversight of this activity to ensure all staff working on their trials had undertaken the trial-specific training required (unless captured in kick-off meeting or investigator meeting attendance records at the start of the trial).

Inspected Organisation's Response – 01 – 3.5.1	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 3.5.1	
	[redacted]
Corrective Action	
Preventative Action 1	
Preventative Action 2	
Effectiveness Check 1	
Effectiveness Check 2	
MHRA Review – 01 – 3.5.1	
[redacted]	
Inspected Organisation's Response – 02 – 3.5.1	
[redacted]	

MHRA Review – 02
Response accepted.

Observations and Recommendations

The following are observations and recommendations to which no response is required.

Pharmacovigilance

- [redacted] version [redacted] effective 20 June 2022 contained incorrect information. It stated 'an AE with an outcome of life-threatening/death was considered unexpected unless the RSI specifically documents that life-threatening/death was a possible outcome of the expected event'. Takeda was reminded that, for an event to be considered expected when fatal or life threatening, it must be explicitly stated as such in the RSI. It was acknowledged that the IB template clarified that if there are expected life-threatening or fatal SARs listed in the RSI, the RSI should include their frequency. However, the incorrect wording in the SOP may have led to errors in the expectedness particularly when RSI was in the SmPC.
- [redacted] was not listed under section 2.3 delegated task of the Takeda GCP Inspection Dossier Clinical Trial spreadsheet despite [redacted] being the holder of the global safety database for [redacted] and currently responsible in collaboration with Takeda of certain activities (e.g. IB and DSUR preparation).

  It was explained in document request [redacted] that Takeda understood this to mean a list of tasks that Takeda was accountable for butt were outsourced by Takeda to a third party service provider. Takeda was reminded that relevant information on delegated tasks (including business partners relationships) should be detailed in the dossier spreadsheet.
- For SAE Case [redacted] it was unclear if this had been reported as a SUSAR. Although, this was not for any of the trials in scope (Study [redacted]) and the Investigator in this case, was the Sponsor of the trial, it was unclear if this had been reported as a SUSAR, and what involvement Takeda had with this.

  It was acknowledged, that the case was not reported to the MHRA by Takeda, as Takeda were not the Sponsor, however, there should be some awareness of what SAEs have been reported as a SUSAR.

Insurance

- No evidence of review of insurance policies was made available to inspectors. As per document request [redacted] evidence of checks for the insurance policy were requested, although 'Regular Renewal Meetings' were mentioned, evidence of these meetings was not provided.

Data Integrity Control Processes

- It was identified that Takeda did not have a requirement for routine audit trail review for the trials in scope. It was noted that there was a new Takeda Audit Trail Review Work Instruction (WI) ([redacted]) which was effective on 08 June 2024. Although not a requirement for Takeda, it was stated that the CRO carried out audit trail review, however, Takeda oversight was not clear.

Training

- It was identified that historical training matrices were not maintained, whilst current training matrices were available. Although Takeda could provide examples where individuals were trained in their roles, there was no documentation to demonstrate that this training was the required training required at that time.

Quality Systems

- Effective dates of SOPs were not always recorded in the revision history of the SOP. Although version numbers and statuses were recorded, this too was inconsistent. The extent of the version history collated was also inconsistent, it was described to inspectors, that some SOPs would have up to 3 previous versions of revision history but some would have more.

  The effective dates were captured in the Document Management System, however when superseded versions were provided, these included the status as superseded and did not contain when they were effective.

Investigator Site 01 – Findings

INSTRUCTIONS TO INSPECTED ORGANISATION

If a separate response is provided by inspected organisation and the investigator site ensure this is clearly differentiated in the responses provided below.

4. Critical Findings

There were **no Critical findings** identified during this inspection.

5. Major Findings

There were 4 **Major findings** identified during this inspection relating to **Medical Oversight by the Principal Investigator**, **eCRF Data / Source Data**, **IMP Management / Pharmacy** and **Project/Trial Management**.

5.1	**Medical Oversight by the Principal Investigator** The medical care given to, and medical decisions made on behalf of, subjects shall always be the responsibility of an appropriately qualified doctor or, when appropriate, of a qualified dentist. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (11)** No person shall - (a)conduct a clinical trial; or (b)perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. **UK Statutory Instrument 2004/1031 (as amended), Part 4, (28)**
5.1.1	There was no contemporaneous evidence of PI assessment of adverse event severity or causality. Participant [redacted] was hospitalised with [redacted] on [redacted] (whilst also suffering with [redacted]). Within the source notes and the site's [redacted] system, there was no documented evidence from the PI or a delegated Sub-Investigator of any severity or causality assessment. This AE was acknowledged and recorded in the eCRF, this was not until [redacted] after it had been entered by the research nurse on [redacted]

Inspected Organisation's Response – 01 – 5.1.1	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 5.1.1	
	[redacted]
Corrective Action	
Preventative Action 1	
Preventative Action 2	
Effectiveness Check 1	
MHRA Review – 01	
Response accepted.	

5.1	Medical Oversight by the Principal Investigator (continued)
5.1.2	There were a number of safety letters which had not been documented as acknowledged by the PI. It was identified as part of document reques[redacted], that within the [redacted] system (which was used to communicate safety letters) there were 158 safety letters which were pending acknowledgement by the PI. See examples below in which the Distribution Status was listed as success, but acknowledgement was listed as Pending (not exhaustive) **AER NO./FILE NAME** **DISTRIBUTION DATE** [redacted] [redacted]

	[redacted] **As part of the response, site to confirm that letters have since been acknowledged and any potential impact on participant safety had been assessed.**

Inspected Organisation's Response – 01 – 5.1.2	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 5.1.2	
	[redacted]
Corrective Action	
Preventative Action	
Effectiveness Check	
MHRA Review – 01 – 5.1.2	
[redacted]	
Inspected Organisation's Response – 02 – 5.1.2	
[redacted]	

MHRA Review – 02
Response accepted.

5.1	Medical Oversight by the Principal Investigator (continued)
5.1.3	There were several examples identified of non-contemporaneous review of bloods.

For Participant [redacted] the following example were identified:

A) Screening haemoglobin was taken on [redacted] but was signed as reviewed on [redacted] by Sub-Investigator [redacted]

B) There was no documentation available to confirm IMP administration stop times, even though this was to be recorded by nursing staff. It was stated that these start and stop times would routinely be recorded on the prescriptions as part of source data:

Participant [redacted]

[redacted]

Inspected Organisation's Response – 01 – 5.1.3

Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 5.1.3	
Corrective Action	[redacted]
Preventative Action 1	
Preventative Action 2	
Preventative Action 3	
Effectiveness Check	

MHRA Review – 01 – 5.1.3
[redacted]

Inspected Organisation's Response - 02 – 5.1.3
[redacted]

Inspected Organisation's Response – 01 – 5.1.3
[redacted]

MHRA Review – 02
Response accepted.

5.2	**eCRF Data / Source Data** The necessary procedures to secure the quality of every aspect of the trial shall be complied with. **Schedule 1, Part 2 (4) UK Statutory Instrument 2004/1031 (as amended)** All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected. **Schedule 1, Part 2 (9) UK Statutory Instrument 2004/1031 (as amended)**
5.2.1	The eCRF entries for concomitant medications were not accurate for Participant [redacted] Participant [redacted] was admitted to hospital from [redacted] Medication detailed on the discharge letter were either missing from or not consistent with the information provided in the eCRF. The following were missing from eCRF but noted on the discharge letter: • [redacted] Medication doses on the discharge letter not consistent with eCRF: • [redacted] There was also a list of medications that should have been stopped, however this was not consistent with the information provided in the eCRF:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

A note in the site's [redacted] system on 16 September 2019 stated that the participant had queried the continuation of [redacted] which pharmacy had confirmed was contra-indicated with [redacted] A query was submitted to Takeda, but pharmacy still advised the participant to omit the Sunday dose of [redacted] until waiting for the sponsor's decision. However, there was no mention of this in the concomitant medication page in the eCRF. It was difficult to reconstruct the outcome, as the inspector was unable to find the query in the file nor the outcome. This was also not accurately reflected in the eCRF.

As part of the response, Sponsor and site to carry out an assessment of medications taken by the participant for any admissions (it may be useful to have a chronological lay out of medication and time), and assess for any contraindications at the time. An assessment should also be carried out by the Sponsor for potential impact on data integrity.

Inspected Organisation's Response – 01 – 5.2.1

Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 5.2.1	
	[redacted]
Corrective Action	
Preventative Action	
Effectiveness Check	
MHRA Review – 01	
Response accepted	

5.3	**IMP Management / Pharmacy** The necessary procedures to secure the quality of every aspect of the trial shall be complied with. **Schedule 1, Part 2 (4) UK Statutory Instrument 2004/1031 (as amended)** Subject to regulation 30, no person shall conduct a clinical trial otherwise than in accordance with— (a) the protocol relating to that trial, as may be amended from time to time in accordance with regulations 22 to 25; **UK Statutory Instrument 2004/1031 (as amended), Regulation 29** All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (9)**
5.3.1	It was not possible to reconstruct how the IMP was stored on the ward prior to administration. It was identified as part of document request [redacted] that temperature monitoring on ward fridges had a built-in system that was displayed on the front of the fridge. Ward staff would make a record of the temperatures on logs but recordings for the period of 2019 and 2020 had been destroyed. Therefore, there was no way to ensure that the IMP was stored as per trial requirements.

Inspected Organisation's Response – 01 – 5.3.1	
Evaluation & Root Cause	[redacted]
Corrective Action	
Preventative Action	
Effectiveness Check	
MHRA Review – 01 – 5.3.1	
[redacted]	
Inspected Organisation's Response - 02 – 5.3.1	
[redacted]	

MHRA Review – 02
Response accepted. It is recommended that Sponsors ensure sites have complied with regulatory and protocol defined document retention requirements.

5.3	**IMP Management / Pharmacy (continued)**
5.3.2	The documentation of training of Pharmacy staff was not robust. A) The Pharmacy Guide Signature Log for the [redacted] dated September 2017 did not refer to what version of the pharmacy guide or protocol staff were trained to. It stated *'I have read and understood the Pharmacy Guide and/or relevant sections of the protocol for the above trial in line with my level of involvement'.* However, there was no way to link to what version of the pharmacy guide or protocol trial staff were trained on. It was of note that there was no version history of the pharmacy guide. In the Pharmacy Site File (PSF), version [redacted] dated September 2019 was filed, but no previous versions were. B) One page of the Pharmacy Guide Signature Log for the [redacted] Trial [redacted] dated September 2017 did not have the trial name section completed. Therefore, if this page got separated, there would be no way to tell what trial it referred to. C) It was identified during the inspection that pharmacists involved in clinical screening did not have GCP training, nor were there any risk assessments completed to assess if GCP training was required.

Inspected Organisation's Response – 01 – 5.3.2	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 5.3.2	
	[redacted]
Corrective Action	
Preventative Action	
Effectiveness Check	
MHRA Review – 01 – 5.3.2	
[redacted]	
Inspected Organisation's Response - 02 – 5.3.2	
[redacted]	

Inspected Organisation's Response – 01 – 5.3.2
[redacted]

MHRA Review – 02
Response accepted. It is expected that all staff involved in clinical trials must understand the minimum requirements for GCP in relation to record keeping and reporting of deviations and adverse events to the trial team. GCP Training can be tailored specific to the role undertaken in relation to the specific trial. This should be reviewed as part of the risk assessment for the trial, with consideration given to GCP awareness training, for example, in the recording of adverse events It may be appropriate to include GCP training as part of the standard induction training for that role/department, thereby ensuring that all staff have a level of GCP training. This general GCP training must be documented and retained.

5.3	IMP Management / Pharmacy (continued)
5.3.3	The documentation relating to the IMP was not robust or representative of site activities. 5.3.3.1) On the Packing list for shipment ID [redacted] dated 09 January 2019, there was a handwritten tick list with no signature or date. In the pharmacy interview, it was confirmed this was written by [redacted] (Pharmacist Technician), but it was [redacted] (Pharmacist Technician) who had signed the accountability log for receipt. 5.3.3.2) The [redacted] receipt documentation was incomplete as the date and record of [redacted] information missing. Although it was noted that a printout of the temperature information was available. 5.3.3.3) The master prescription signed by the PI was not dated. Therefore, it was unable to be determined when the PI had reviewed it. 5.3.3.4) There was no reference to protocol version on the master prescription where information was taken from. 5.3.3.5) For the [redacted] worksheet, for several examples, there was no requirement to record time of reconstitution, even though the 8 hour expiry was based on this. The expiry date was handwritten on the label, but there was no way to reconstruct that this was correct. 5.3.3.6) For Participant [redacted] the final release of IMP was signed by [redacted] It was confirmed that [redacted] was in fact [redacted] on the training log but there was no details of their name change. 5.3.3.7) There was no chain of custody for the IMP leaving pharmacy and being accepted by nurses on the ward. Although it was described in the facilities tour that this was receipted by nursing staff, on discussion with the pharmacy team it was confirmed that these records had been destroyed. 5.3.3.8) The front cover of the worksheet file [redacted] dated December 2018 for participant [redacted] had a master prepared by [redacted] (Pharmacy Technician) but the approved by

		section had not been completed.
	5.3.3.9)	Examples were identified of Aseptic Dispensing Unit worksheets that had not been completed. For participant [redacted] or both the [redacted] doses there was no date of preparation on the worksheet. For [redacted] the calculation check was dated as being completed on 07 October 2019, which would have been prior to preparation date.

Inspected Organisation's Response – 01 – 5.3.3	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 5.3.3
[redacted]

Inspected Organisation's Response – 01 – 5.3.3	
	[redacted]
Corrective Action 1	
Corrective Action 2	
Corrective Action 3	
Preventative Action 1	
Preventative Action 2	
Preventative Action 3	
Preventative Action 4	
Preventative Action 5	

Inspected Organisation's Response – 01 – 5.3.3	
Preventative Action 6	[redacted]
Preventative Action 7	
Effectiveness Check	
MHRA Review – 01 – 5.3.3	
[redacted]	
Inspected Organisation's Response - 02 – 5.3.3.	
[redacted]	

MHRA Review – 02
Response accepted.

5.4	**Project / Trial Management** The rights, safety, and well-being of the trial subjects are the most important considerations and shall prevail over interests of science and society. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (1).** No person shall – (a) conduct a clinical trial; or (b) perform the functions of the sponsor of a clinical trial (whether that person is the sponsor or is acting under arrangements made with that sponsor), otherwise than in accordance with the conditions and principles of good clinical practice. **UK Statutory Instrument 2004/1031 (as amended), Regulation 28 (1)** …Sponsor of a clinical trial shall put and keep in place arrangements for the purpose of ensuring that with regard to that trial the conditions and principles of good clinical practice are satisfied or adhered to. **UK Statutory Instrument 2004/1031 (as amended), Regulation 28 (2)** All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (9)** The necessary procedures to secure the quality of every aspect of the trial shall be complied with. **UK Statutory Instrument 2004/1031 (as amended), Schedule 1, Part 2, (4).**
5.4.1	Documentation of calibration records of equipment used throughout the trial was not robust. A) It was identified that the height measuring rulers on the [redacted] were not on the records for the Electronics and Medical Engineering (EME) team, and therefore there was no evidence of calibration or maintenance available. The height would have been used to calculate the [redacted] for participants in order to calculate the doses of IMP. B) ECG machine (Asset ID [redacted]) calibration certificates were not supplied as part of document request [redacted] **As part of the response, site to confirm if this ECG machine was used during trial conduct and if so, to confirm the machine had appropriate calibration records in place.**

Inspected Organisation's Response – 01 – 5.4.1	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 5.4.1	
	[redacted]
Corrective Action	
Preventative Action	
Effectiveness Check 2	
MHRA Review – 01	
Response accepted	

6. Other Findings

There were **3 Other findings** identified during this inspection, relating to **Laboratory Facilities and Equipment**, **eCRF Data / Source Data**, and **Informed Consent**.

6.1	**Laboratory Facilities and Equipment**
6.1.1	There was no evidence provided to the inspector of any Sample Processing Logs for this trial at site. Therefore, there was no way to verify that samples had been processed as per the Sample Management Plan or Protocol. It was described as part of document request [redacted] that samples would have been spun according to the protocol by a nurse and samples collected as previously arranged by [redacted] However, no documentation could demonstrate this.

Inspected Organisation's Response – 01 – 6.1.1	
Evaluation & Root Cause	[redacted]
Corrective Action 1	
Preventative Action	
Effectiveness Check	
MHRA Review – 01 – 6.1.1	
[redacted]	

Inspected Organisation's Response – 01 – 6.1.1
Inspected Organisation's Response - 02 – 6.1.1
[redacted]

MHRA Review – 02
Response accepted.

6.2	eCRF Data / Source Data
6.2.1	The Eligibility Verification Form [redacted] dated 12 October 2018 did not have any reference to the protocol from which it was derived.

Inspected Organisation's Response – 01 – 6.2.1	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 6.2.1	
	[redacted]
Corrective Action	
Preventative Action	
Effectiveness	
MHRA Review – 01 – 6.2.1	
[redacted]	
Inspected Organisation's Response - 02 – 6.2.1	
[redacted]	

MHRA Review – 02
Response accepted.

6.2	eCRF Data / Source Data (continued)

6.2.2	Examples were identified at site in which source documentation was not adequately recorded, with examples of incorrect, missing and inconsistent documentation: A) The Source worksheet used for [redacted] onwards [redacted] dated 21 September 2018, had site [redacted] initially, but had been crossed out on page one only and amended to [redacted] B) It was difficult to reconstruct the trial data/information for participant [redacted] It seemed there were several missing documented visits and notes were not chronological. On discussion with the team, there was another system which documented all trial visits and included trial related communications. This was the [redacted] system which was not included as part of the Source data agreements completed by site and signed by PI. C) Some entries in the [redacted] system, for example entry on 20 June 2019, did not always reference the clinical trial, even though participant vital signs were taken and were related to trial activity. D) There was inconsistency within the source notes. In the original main notes, for participant [redacted] there was a clinic note dated [redacted] which contained medical history and social history due to an admission to the Emergency Department. 2 copies of this were taken and filed in various parts of the participant's trial file. The copy in the screening file was verbatim. However, the copy in the general notes section had a handwritten date underneath it of [redacted]. **As part of the report response, site to review and investigate with the correct dates of admission.**

Inspected Organisation's Response – 01 – 6.2.2	
Evaluation & Root Cause	[redacted]

Inspected Organisation's Response – 01 – 6.2.2	
	[redacted]
Corrective Action	[redacted]

Inspected Organisation's Response – 01 – 6.2.2	
Preventative Action 1	[redacted]
Preventative Action 2	
Preventative Action 1	
Effectiveness Check	
MHRA Review – 01	
Response accepted	

6.2	**eCRF Data / Source Data**
6.2.3	Examples were identified where data in the eCRF did not accurately reflect the source. For participant [redacted] was performed on 17 July 2019. Entries on the 'Adult Observation Chart' did not match the entries on the eCRF. This was compounded by data being entered prior to the visit.

Vital Sign	Paper Chart	eCRF	Entered By
Temperature	[redacted]	[redacted]	Research Nurse [redacted] on 16 July 2019 11:47
Heart Rate	[redacted]	[redacted]	Research Nurse [redacted] on 25 July 2019
Systolic BP	[redacted]	[redacted]	Research Nurse [redacted] on 25 July 2019
Diastolic BP	[redacted]	[redacted]	Research Nurse [redacted] on 25 July 2019

Inspected Organisation's Response – 01 – 6.2.3	
Evaluation & Root Cause	[redacted]
Corrective Action	
Preventative Action	
Effectiveness Check	
MHRA Review – 01 – 6.2.3	
[redacted]	
Inspected Organisation's Response - 02 – 6.2.3	
[redacted]	

MHRA Review – 02
Response accepted.

6.3	Informed Consent
6.3.1	An example was identified of a staff member taking informed consent when not appropriately delegated to do so. For Participant [redacted] Sub-I) had taken consent for participant [redacted] on 18 June 2019 but was not delegated for taking consent until 19 June 2019.

Inspected Organisation's Response – 01 – 6.3.1	
Evaluation & Root Cause	[redacted]
Corrective Action	
Preventative Action 1	

Inspected Organisation's Response – 01 – 6.3.1	
	[redacted]
Preventative Action 2	
Preventative Action 3	
Effectiveness Check	
MHRA Review – 01	
Response accepted	

6.3	Informed Consent (continued)
6.3.2	An example was identified of the informed consent form not being adequately completed. For Participant [redacted] he section agreeing that the participant's doctor will be told about the participant taking part, and they may give the study doctor information about health was left blank. There was an option to tick yes or no, although initialled by patient, this yes/no box was empty. This was signed by [redacted] on [redacted] As part of the response, Site to review informed consents and ensure they are completed correctly and prior to GP letter being sent to participants GP informing them of Study participation.

Inspected Organisation's Response – 01 – 6.3.2	
Evaluation & Root Cause	[redacted]
Corrective Action 1	

Inspected Organisation's Response – 01 – 6.3.2	
Preventative Action 1	[redacted]
Effectiveness Check 2	
MHRA Review – 01 – 6.3.2	
[redacted]	
Inspected Organisation's Response - 02 – 6.3.2	
[redacted]	

MHRA Review – 02
Response accepted.

Observations and Recommendations

The following are observations and recommendations to which no response is required.

Record Keeping / Essential Documents

- In the participant notes for Participant [redacted] the section for the Randomisation email contained vital sign records on [redacted] but no randomisation email.

Report Author:

[redacted]

GCP Inspector, Compliance Team 1, Standards and Compliance, MHRA

Report Reviewer:

[redacted]

[redacted] GCP Inspector, Compliance Team 1, Standards and Compliance, MHRA

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.

Appendix I Summary of Activities

Inspected Organisation

Clinical Trial	Assessed			Comment
	Yes	Partial	No	
[redacted]		✓		Project management, monitoring, selected review of TMF
[redacted]		✓		Pharmacovigilance, selected review of TMF
[redacted]		✓		Quality Assurance and vendor oversight, selected review of TMF
[redacted]		✓		training, selected review of TMF
[redacted]		✓		Pharmacovigilance

Activity	Assessed			Comment
	Yes	Partial	No	
Analytical Laboratory			✓	
Archiving		✓		As part of Project Management
BE/ BA Activities			✓	
Clinical Pathology Laboratory			✓	
Clinical Trial Reporting			✓	
Computerised Systems		✓		As part of Project Management

Contracts & Agreements		✓		
Data Management		✓		
eCRF / Diaries / IVRS		✓		As part of Project Management and Investigator Site
IMP Management		✓		As part of Project Management and Investigator Site
Medical Affairs			✓	
Monitoring		✓		As part of Project Management and Training
Pharmacovigilance	✓			
Project Management	✓			
Quality Assurance	✓			
Quality Systems		✓		
R&D Unit (Non-commercial only)			✓	
Regulatory Affairs		✓		As part of Project Management
Statistical Analysis			✓	
Technical Facility (i.e. x-ray)			✓	
Training	✓			
Trial Master File/Essential Documents		✓		Selected review of TMF
Other			✓	

Investigator Site 01

Activity	Assessed			Comment
	Yes	Partial	No	
Principal Investigator	✓			
Research Nurse	✓			
Sub-Investigator			✓	

Laboratory		✓		As part of facilities tour and selected document review
IMP Management / Pharmacy	✓			
Consents		✓		For selected participants
CRFs, eCRFs, Participant Diary, IVRS		✓		For selected participants
Source Data		✓		For selected participants
Site Master File		✓		Selected review
Technical Facility (i.e. x-ray)		✓		Facilities tour conducted
Other			✓	

Appendix II

Inspection Closing Statement

GCP INSPECTION STATEMENT

Inspection & Organisation Information	
Inspection Number	Insp GCP 16189/19142243-0002
Purpose of Inspection	Statutory GCP Systems
Type of Inspection	Remote
Organisation Inspected	Takeda Development Centre Europe Ltd (Takeda)
Organisation Address	1 Kingdom Street, London. W2 6BD
Organisation Type	Commercial
Dates of Inspection	Day 1: 06 June 2024 Days 2 to 6: 10 to 14 June 2024 Total 5 days over 6 days.
Lead Inspector	[redacted] GCP Inspector [redacted]
Accompanying Inspector(s)	[redacted] [redacted] GCP Inspector [redacted] [redacted] GPvP Inspector [redacted]
Date of Inspection Statement	05 January 2026

The organisation has provided corrective and preventative actions in response to the inspection report. These have been reviewed by the GCP Inspectorate and are considered acceptable. This inspection can be considered closed.

As detailed in the inspection report the organisation is required to submit details of impact assessments as per Findings 2.5.1 and 6.3.2 via email to the Lead Inspector.

In summary:

There was 1 “critical” findings identified during this inspection relating to:

- Pharmacovigilance

There were 5 “major” findings identified during this inspection relating to:

- Quality Systems
- Serious Breach Reporting
- Training
- Project / Trial Management
- Pharmacovigilance.

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

Statement Issued by

[redacted]

GCP Inspector, Compliance Team 1, Standards and Compliance, MHRA