



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Safety reporting in CTIS

Webinar for SMEs and Academia on the Clinical Trial Regulation (Regulation (EU) No 536/2014) and the Clinical Trials Information System (CTIS)

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An agency of the European Union





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1. Future changes to clinical trial safety reporting
2. Submission of Annual Safety Reports
3. EU Network cooperation



Future changes to clinical trial safety reporting

- CTR demands electronic submission of SUSARs and ASRs
- SUSARs will be submitted to the EudraVigilance database (EV CTM)
- ASRs will be submitted via CTIS
- COM will adopt implementing regulation
- saMS will assess safety relevant data substance based
- Communication between MSs and with sponsors will be via CTIS (ASR, ad hoc assessment, corrective measures)
- IT support not yet fully developed, will be further developed post go live
- CTFG will develop and adapt internal guidance

SUSAR:

- SUSARs to EV unless the NCA requires direct reporting
- Reporting obligations as of CT-3 to investigators and ECs according to national legislations in MSs with CTs within Directive

ASR:

- With first trial for a substance under the CTR: ASR to CTIS
- Informative cover letter essential: name all MSCs for ongoing CTs in EU/EEA within Directive and CTR.
- Obligation as of CT-3 to investigators (new safety data or change in B/R) and ECs according to national legislations in MSs with ongoing CTs within Directive remains



Submission of Annual Safety Reports

Initiate ASR submission (ASR submitter)

Clinical trials

There is no save button; make sure you have all documents available before you start

Clinical trials Notices & alerts 7 Annual safety reporting RFI User administration

Annual safety reports



Enter EU CT or ASR ID or use advanced search. To search for multiple IDs, separate them with co

SEARCH

Advanced Search ▾

Submit ASR

↑ CLEAR

✓ CHECK

✕ CANCEL

SUBMIT

Download

+ NEW ASR

1

Sponsor information

2

Clinical Trial detail

3

ASR reporting period details

4

Supporting documents and submit

Expand all ▾

▼ Step 1

Sponsor information

▼ Step 2

Clinical Trial Detail

▼ Step 3

ASR Reporting Period details

▼ Step 4

Supporting Documents and Submit

Submitted:
24/11/2021

Sponsor:
Achilles - testcompany

saMS:

1 of 1 pages

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1. Enter Sponsor Information

▲ Step 1

Sponsor information



EUROPEAN MEDICINES AGENCY

Organisation details of the selected sponsor

☐ This ASR is a consolidated report following a co-development agreement

Organisation responsible for the ASR submission *

Organisation name

Tick boxes for co-development and sponsor status (commercial)

Address

Address 2

Contact details for ASR submission

Address 3

Full name *

Address 4

☐ Contact or legal representative is same from sponsor

Post Code

Organisation name *

City

Address *

Country

Email address *

Phone Number

Phone Number *

☐ Are any of the sponsors or co-sponsors commercial
(Select if the sponsor or any of the co-sponsors are commercial)

Make sure all clinical trials for the IMP selected are included in ASR submission

Contact details for ASR submission

Drop down menu provides sponsor information according to affiliation

Address details are auto-populated by selecting an organisation

Partially auto-populated if identical affiliation is selected

Phone number without interpunction

Section contact details for ASR submission shows mandatory fields when opened

2. Enter Clinical Trial Details

Step 2

Clinical Trial Detail

+ Search clinical trial

Select the IMP(s) and AxmP(s) of your clinical trial selection

Search trials

Product name

Active substance

ATC code

Pharmaceutical form

Strength

EU MP number

Marketing Authorisation Number

EU substance

EU CT number

Medical condition

Member States

Status

Sponsor

All
AUTHORISED
ENDED
HALTED

All
Austria
Belgium
Bulgaria



Testing 123

EU CT number 2021-500220-21-00

Decision date

Sponsor

Achilles - testcompany

MS

Austria

Clear

Search

Search for CTs related to your organisation (at least 3 letters)

In a further step tick the products for the ASR

In the pop up select the CTs the ASR is submitted for and push „Add to ASR“

3. Enter ASR reporting period details

Is this the sponsor's first ASR for any of the IMP(s) selected?

☐ Yes ☐ No

If yes, indicate which IMPs

KEYTRUDA 50 mg powder for concentrate for solution for infusion
Aspirin Complex Forró Ital 500 mg/ 30 mg granulátum belsőleges szu:
Aspirin Complex Forró Ital 500 mg/ 30 mg granulátum belsőleges szu:

Data lock point

📅

ASR reporting period *

No technical validation for the dates entered in the system

dd/mm/yyyy

📅

dd/mm/yyyy

📅

RSI Updated during the reporting period *

☐ Yes ☐ No

RSI changes submitted and approved in SM?

Substantial modification on RSI submitted and approved during the reporting period *

☐ Yes ☐ No

During the reporting period ASR includes *

Premature ended trial/s	Novel novel combination
Unexpected event changing benefit risk of any trial	New combination
Substantial modification of protocol or IB for risk mitigation any trial	First in class product/IMP(in EU)
Refused approval due to safety reason	Advanced therapy medicinal product (ATMP)
Serious breach safety related or impact on safety	New signals or concerns or risk for the product
Urgent safety measure	Temporary halt or suspension of any trial due to safety reason
Other	
None	

More than one information criterion can be selected

4. Upload documents and submit

Step 4

Supporting Documents and Submit



ASR Document *

SmPC

(if the SmPC includes RSI and not submitted as part of the ASR document)

Investigator's Brochure

(if the Investigator's Brochure includes RSI and not submitted as part of the ASR document)

Other

Submit

Only mandatory, single document slot, limited file size, PDF

multiple documents are possible for those slots (old and new version)

Include cover letter (essential especially for transition requirements) here

Documents are not published

I, on behalf of the sponsor, confirm that the:

1. Information provided is complete
2. Attached documents contain an accurate account of the information available
3. The Sponsor, Achilles - testcompany, declares that the Annual Safety Report is prepared and hereby submitted to the Agency in accordance with Article 43 of Regulation (EU) No 536/2014 and all other applicable legal provisions.

☐ * RSI Document/s (Old and new version where applicable)

☐ * I agree with the above statements

Add document

Document upload

Title	Type	Date	Language	Version	System version	Actions
ASR	ASR Document	24/11/2021	English	1	1.00	

Place documents here or click to upload
9_Authorisation_doc.pdf

Title*

ASR

Type*

ASR Document

Language

English

Version*

1

System version

1.00

Date*

24/11/2021

Comment

Remove

This document will not be publicly accessible.

Cancel

Attach

For submission scroll to the top of the page

CLEAR

CHECK

CANCEL

SUBMIT

Find the RFIs according to type in the RFI tab

Clinical trials Notices & alerts 3 Annual safety reporting RFI User administration

SEARCH [Advanced Search ▾](#)

MSC

Status

Submit Date

Source type

Assess ASR ✕ Add Source type

Adhoc Assessment
Corrective measures
Initial
Subsequent addition of MSC
Substantial modification

Response Date

CLEAR

SEARCH

Showing 1 - 1 of 1 items 1 of 1 pages < 1 >

Sort by: No sorting ▾

RFI-ASR-2021-00001-001	MSC	Source type	Evaluation process	Submitted	Responded	Due
Pending ASR-2021-00001	Austria	Assess ASR		24/11/2021		08/12/2021
IMP1: Aspirin Complex Forró Ital 500 mg/ 30 mg granulátum belsőleges szuszpenzióhoz · PSEUDOEPHEDRINE HYDROCHLORIDE, ACETYLSALICYLIC ACID						
IMP2: Aspirin Complex Forró Ital 500 mg/ 30 mg granulátum belsőleges szuszpenzióhoz · PSEUDOEPHEDRINE HYDROCHLORIDE, ACETYLSALICYLIC ACID						

- Open RFI advanced search
Select the RFI **source type** „Assess ASR”
- Select **status** “Pending”
- View submission date and due date
- Sort search results by many different criteria

No sorting

Source type
Evaluation process
EUCT number
MSC
Submit Date
Due date
Response Date
Status

- Click on RFI number to respond directly

Respond to the RFI and attach missing/supporting documents

ASR-2021-00001

Achilles - testcompany

IMP: Aspirin Complex Forró Ital 500 mg/ 30 mg granulátum belső szuszpenzióhoz, Aspirin Complex Forró Ital 500 mg/ 30 mg granulátum szuszpenzióhoz, KEYTRUDA 50 mg powder for concentrate for solution
Submitted: 24/11/2021

ASR Submission Assessment

Respond to RFI

REQUEST FOR INFORMATION - RFI-ASR-2021-

CONSIDERATIONS

ID: RFI-ASR-2021-00001-001-01

Please explain

Sponsor response:

RESPOND

Respond to considerations directly via the chat field and add documents if needed

DOCUMENTS

MS Documents



MS supporting

English · Additional
Submission data
Version 1 · 24/11/2021

Sponsor Documents

I, on behalf of the sponsor, confirm that the:
a) Information provided is complete
b) Attached documents contain an accurate account of the product
c) No personal data included
☒ I agree with the above statements

Document upload

Place documents here or click to upload

9_Authorisation_doc.pdf

Title*

Sponsor response

Type*

Additional Document

ASR Document

Investigator Brochure

Protocol

Sponsor Discussion Response Supporting Document

Summary of Product Characteristics (SmPC)

Language

English

Date*

24/11/2021

Comment

Remove

Cancel

Attach

Add document

Submit

CONSIDERATIONS

ID: RFI-ASR-2021-00001-001-01

Please explain

Multiple question rounds possible if need
After satisfactory response to the RFIs the MSs finalise the assessment

RESPOND

End of assessment information available for the sponsor

Clinical trials

Notices & alerts

Annual safety reporting

RFI

ASR-2021-00001

Achilles - testcompany

IMP: Aspirin Complex Forró Ital 500 mg/ 30 mg granulátum belsőleges szuszpenzióhoz, Aspirin Complex Forró Ital 500 mg/ 30 mg granulátum belsőleges szuszpenzióhoz, KEYTRUDA 50 mg powder for concentrate for solution for infusion
Submitted: 24/11/2021

MSC
AT

saMS
Austria

ASR reporting period
24/11/2020 - 23/11/2021

Finalised
24/11/2021

Enter EU CT or ASR ID or use advanced search

Advanced search

Product name:
Type free text

Pharmaceutical form:

Assessment status:

Member states:

ASR Submission

Assessment

Respond to RFI

Summary and conclusion for sponsor

Are there any new issues?*

Acceptable action is taken by sponsors?*

Specific action is required by sponsors*

Due date for specific action?*

Requested action*

Use advanced search to find ASRs according to assessment status

Clear

Search ASRs

Download

+ NEW ASR

Showing 1 - 2 of 2 items

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< 1 >

Sort by: 1

ASR-2021-00001

finalised

Submitted: 24/11/2021

Sponsor: Achilles - testcompany

saMS: Austria

IMP: Aspirin Complex Forró Ital 500 mg/ 30 mg granulátum belsőleges szuszpenzióhoz, IMP: A...

ASR-2021-00000

submitted

Submitted: 24/11/2021

Sponsor: Achilles - testcompany

saMS:

IMP: Metoject PEN 27,5 mg injekční roztok v předplněném peru, IMP: Ibuprofen 200 mg tablet...

Showing 1 - 2 of 2 items

1 of 1 pages

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Summary and conclusion for the sponsor:

- New issues
- Acceptability of sponsor actions
- Required sponsor actions
- Due date (if applicable)
- Requested action (if applicable)

The sponsor does not receive the assessment reports



EU Network cooperation

Article 44.2 of the CTR allows COM to set up and modify rules for cooperation in the assessment of SUSARs and ASRs. New concepts were created:

- Safety assessing Member state (saMS)
- saMS is in charge of the surveillance for a substance (all SUSARs and ASR for all trials)
- saMS develops general recommendations in relation to safety concerns
- RMS/MSCs implement them if applicable to their trials via corrective measures
- Cooperation between saMS, RMS and MSCs in CTs using the same active substance
- IT support not yet fully developed
- CTFG develops internal guidance for assessment and work around to overcome missing IT support



Any questions?

Further information

emaevents@diaglobal.org (CTIS sponsor Master Trainer programme)

CT.Sponsortraining@ema.europa.eu (general queries on other (sponsor) training)

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Article 42: **Reporting of suspected unexpected serious adverse reactions by the sponsor to the Agency** (abbreviated and adapted wording)

1. The sponsor shall **report electronically** all SUSARs to IMPs occurring in that clinical trial, **irrespective of location of occurrence** (in the Union or in a third country) **regardless of pharmaceutical form and strength or indication** investigated, even after the EOT.
2. The reporting period for SUSARs if **fatal or life-threatening** as soon as possible not later than **7 days**, if **non-fatal or non-life-threatening** not later than **15 days** after becoming aware; if initially non-fatal or non life threatening turning into fatal or life-threatening, as soon as possible not later than 7 days after this change. Where necessary submit an initial incomplete report followed up by a complete report.
3. Where a sponsor does not have the possibility to report to EV and with MS agreement it may report to the MS where the SUSAR occurred. That Member State shall report to EV.

Article 43: **Annual reporting by the sponsor to the Agency**

1. Regarding investigational medicinal products other than placebo, the sponsor shall submit **annually** through the database referred to in Article 40(1) to the Agency a **report on the safety of each investigational medicinal product** used in a clinical trial for which it is the sponsor.
2. In the case of a clinical trial involving the use of **more than one investigational medicinal product**, the sponsor may, if provided for in the protocol, submit a **single** safety **report** on all investigational medicinal products used in that clinical trial.
3. The annual report referred to in paragraph 1 shall only contain **aggregate and anonymised data**.
4. The obligation referred to in paragraph 1 starts with the first authorisation of a clinical trial in accordance with this Regulation. It **ends with the end of the last clinical trial** conducted by the sponsor with the investigational medicinal product.

Article 44: **Assessment by Member States**

1. The Agency shall, by electronic means, forward to the Member States concerned the information reported in accordance with Article 42 and 43.
2. **Member States shall cooperate in assessing** the information reported in accordance with Articles 42 and 43. The **Commission** may, by means of implementing acts, **set up and modify the rules on such cooperation**. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 88(2).
3. The responsible **ethics committee shall be involved** in the assessment of the information referred to in paragraphs 1 and 2, **if it has been provided for in the law of the Member State concerned**.



Reference Safety information (RSI)

Reporting of AEs/ARs: Provide worldwide unique case identification number

Annual Safety Reports: Provide patient numbers in SAE tables

Safety Issues of AxMPs: authorised AxMPs to EVPM, non-authorised AxMPs to EVCTM

Safety during Transition Period of Clinical Trials Regulation (EU) No 536/2014

Implementation:

With first trial for a substance under the CTR: ASR to CTIS (name all MSCs for ongoing CTs in EU/EEA within Directive and CTR). Obligation as of CT-3 to investigators (new safety data or change in B/R) and ECs according to national legislations in MSs with ongoing CTs within Directive remains.

SUSARs to EV unless the NCA requires direct reporting. Reporting obligations as of CT-3 to investigators and ECs according to national legislations in MSs with CTs within Directive