# *Homeclinical trials -* How to identify easily AESI?

### Grade 3 or above “electrocardiogram QT corrected interval prolonged”

The average QTcF value should be calculated after each ECG (scheduled or unscheduled). If more than 2 ECGs were performed, the average QTcF is the arithmetic mean of the 2 longer QTcF. If the average QTcF corresponds to grade 3 or 4 meaning ≥501 msec (above or equal to 501) with or without symptoms, then **please report as AESI**. If the expert review concludes that your QTcF calculation is incorrect, then we can change the AE status later.

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| **Condition term** | **NOT AESI** | | **AESI** | |
| **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| Electrocardiogram QT Corrected Interval Prolonged | Average QTcF 450 - 480 ms | Average QTcF 481 - 500 ms | Average QTcF >= 501 ms without signs/symptoms of serious arrhythmia | Average QTcF >= 501 or >60 ms change from baseline and one of the following: Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia |

### Grade 3 or above leukopenia (incl. neutropenia, lymphopenia, etc.), anemia or thrombocytopenia

The grade should be checked for all blood count abnormalities after each test (scheduled or unscheduled). If at any time, the WBC is less than 2 x10E9/L **and/or** the hemoglobin is less than or equal to 7.9 g/dL **and/or** the platelets are less than or equal to 49.9 x10E9/L., then **please report as AESI**. If **only one** of these is grade 3 or 4 it is an AESI. If one white blood cell line is considered a grade 3 or 4 (e.g. neutropenia grade 4, 0.20 x10E9/L), **please also report as AESI**.

**What if I think it is a lab error?**  If you have doubts about the lab results, please re-order a test as soon as possible to confirm the results and report if the abnormality is confirmed. If the re-test cannot be done immediately, please report. If it was a lab error then the result is invalid, not recordable, not reportable and will be discarded as an AE/AESI.

| **Condition term** | **NOT AESI** | | **AESI** | |
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| **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| Anaemia | 10.5 - 9.5 g/dL [105 - 95 g/L] | 9.4 - 8.0 g/dL  [94 - 80 g/L] | 7.9 - 6.5 g/dL  [79 - 65 g/L] | < 6.5 g/dL  [< 65 g/L] |
| Platelets Decreased | 99,999-75,000/mm3  [99.9-75.0 x10^9/L] [99.9-75.0 x10^3/μL] | 74,999-50,000/mm3  [74.9-50.0 x10^9/L] [74.9-50.0 x10^3/μL] | 49,999-20,000/mm3 [49.9-20.0 x10^9/L] [49.9-20.0 x10^3/μL] | <20,000/mm3  [<20.0 x10^9/L] [<20.0 x10^3/μL] |
| White Blood Cell Decreased | <LLN - 3000/mm3 [<LLN - 3 x10^9/L] [<LLN - 3 x10^3/μL] | <3000 - 2000/mm3 [3 - 2 x10^9/L] [3 - 2 x10^3/μL] | <2000 - 1000/mm3 [<2 - 1 x10^9/L] [<2 - 1 x10^3/μL] | <1000/mm3 [<1 x10^9/L] [<1 x10^3/μL] |
| Absolute Neutrophil Count Low | 1500 - 1000/mm3 [1.5 - 1.0 x10^9/L] [1.5 - 1.0 x10^3/μL] | 999 - 750/mm3  [0.99 - 0.75 x10^9/L] [0.99 - 0.75 x10^3/μL] | 749 - 500/mm3  [0.74 - 0.50 x10^9/L] [0.74 - 0.50 x10^3/μL] | <500/mm3  [<0.50 x10^9/L] [<0.50 x10^3/μL] |
| Lymphocyte Count Decreased | <LLN - 800/mm3 [<LLN - 0.8 x 10^9/L] [<LLN - 0.8 x10^3/μL] | <800 - 500/mm3 [<0.8 - 0.5 x10^9/L] [0.8 - 0.5 x10^3/μL] | <500 - 200/mm3 [<0.5 - 0.2 x10^9/L] [<0.5 - 0.2 x10^3/μL] | <200/mm3 [<0.2 x 10^9/L] [<0.2 x10^3/μL] |

### Grade 3 or above peripheral neuropathy

If during a scheduled or unscheduled peripheral neuropathy screening (e.g. triggered by patient complaining of pins and needles), the scores you obtain from Brief Peripheral Neuropathy Screening Test and/or the symptoms suggest or confirm a grade 3 or 4 peripheral neuropathy (see also SOP SP-018-CT), then **please report as AESI**.

* Example 1, patient reports severe subjective symptoms (grade 3 Paresthesia) and mildly abnormal vibration perception and reflexes (grade 1 Neurosensory disorder) 🡪 **report peripheral neuropathy grade 3=AESI.**
* Example 2, patient reports mild subjective symptoms (grade 1 Paresthesia) and severely abnormal vibration perception and areflexia (grade 4 Neurosensory disorder) 🡪 **report peripheral neuropathy grade 4=AESI.**
* Example 3, patient reports severe subjective symptoms (grade 3 Paresthesia) and normal vibration perception and normal reflexes 🡪 **report paresthesia grade 3, investigate and manage, repeat the test or refer to a neurologist as appropriate=AE.**
* Example 4, patient reports no subjective symptoms, normal vibration perception and mild hyporeflexia (grade 1 neurosensory disorder) 🡪 **report hyporeflexia grade 1, investigate and manage, repeat the test or refer to a neurologist as appropriate=AE.**

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| **Condition term** | **NOT AESI** | | **AESI** | |
| **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| Neuro-Sensory Disorders | Mild impairment in sensation (decreased sensation, e.g. vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing; and/or vibration perception score 1 (mild loss). | Moderate impairment (mod decreased sensation, e.g. vibratory, pinprick, hot/cold to ankles) and/or joint position; and/or vibration perception score 2 (moderate loss). | Severe impairment (decreased or loss of sensation to knees or wrists); and/or vibration perception score 3 (severe loss) and/or deep tendon reflex score 1. | Sensory loss involves limbs and trunk; paralysis; or seizures; and/or deep tendon reflex score 0. |
| Paresthesia (Burning, Tingling, etc.) | Mild discomfort; no treatment required; | Moderate discomfort; non-narcotic analgesia required; and/or BPNS subjective sensory neuropathy score 4-6 on any side. | Severe discomfort; or narcotic analgesia required with symptomatic improvement; and/or BPNS subjective sensory neuropathy score 7-10 on any side. | Incapacitating; or not responsive to narcotic analgesia. |

It is recommended to use the ‘diagnosis term’ from the protocol as much as possible when peripheral neuropathy occurs, meaning: *Peripheral neuropathy* instead of the symptoms (burning, tingling, loss of sensation, etc.). You can add the location and some adjectives as needed, e.g. peripheral neuropathy in lower limbs.

**How to report if we are not sure or pending investigations?** Please do not wait to confirm your suspicions. **If the investigations are not fully conclusive but you still suspect peripheral neuropathy, please report**.

* Example 1, patient has severe pain in knee joints on 01-Feb-2018; you think it is arthralgia initially. Then you perform BPNS and diagnose peripheral neuropathy on 05-Feb-2018. 🡪 report on 05/06 Feb as AESI diagnosed on 05-Feb.
* Example 2, patient reports severe pains in limbs on 01-Feb-2018, but cannot come to the site before 05-Feb-2018, he went very far to visit his family; on 05-Feb-2018 you perform BPNS and the result is not conclusive, but you still suspect LZD-induced neuropathy and interrupt this drug. 🡪 report on 05/06 Feb as AESI as you suspect neuropathy. If later, it turns out it is not neuropathy but another cause, we can change the status of the AE at follow-up.

### Grade 3 or above optic neuritis

If during a scheduled or unplanned ophthalmological assessment (e.g. if patient complains of blurry vision), the symptoms and/or the acuity measured are in favour of optic nerve disorder and match the definition of a grade 3 or 4, then **please report as AESI**.

It is recommended to use the ‘diagnosis term’ from the protocol as much as possible when optic nerve disorder occurs, meaning: *Optic neuritis* instead of the symptoms (vision colour abnormal, decrease visual acuity, blindness on right, etc.). You can add lateralization and adjectives as needed, e.g. Optic neuritis bilateral.

If patient is not colour blind at baseline and the Ichihara test becomes abnormal, it is an early indicator of possible optic neuritis, but visual acuity (not number of plates) allow for the grading of optic neuritis.

**How to report if we are not sure or pending investigations?** Please do not wait to test to confirm your suspicions. If the investigations are not conclusive but you still suspect optic neuritis and visual acuity is impacted (worse than 20/40), please report. If another cause is found later, we can change the AE status at this stage.

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| **Condition term** | **NOT AESI** | | **AESI** | |
| **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| Optic Nerve Disorder | Asymptomatic; clinical or diagnostic observations only | Limiting vision of the affected eye (20/40 [6/12; 70%] or better) | Limiting vision in the affected eye (worse than 20/40 [6/12; 70%] but better than 20/200 [6/60 ; 10%]) | Blindness (20/200 [6/60; 10%] or worse) in the affected eye |

### Hepatotoxicity

The grade should be checked for blood biochemistry abnormalities after each test (scheduled or unscheduled). Verify if liver function test results match the AESI definition:

In endTB-Q and endTB protocol version 3+:

* Increases in ALT or AST ≥5x ULN.

In endTB protocol versions 1-2:

1. increases in ALT or AST ≥5x ULN,
2. increases in ALT or AST ≥3x ULN with clinical manifestations, or
3. increases in ALT or AST ≥3x ULN with concomitant increase in bilirubin [total bilirubin] ≥1.5 x ULN.

**What if I think it is a lab error?**  If you have doubts about the lab results, please re-order a test as soon as possible to confirm the results and report if the abnormality is confirmed. If the re-test cannot be done immediately, please report. If it was a lab error then the result is invalid, not recordable, not reportable and will be discarded as an AE/AESI.

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| **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** |
| Alanine Aminotransferase (ALT or SGPT) Increased | >ULN - 3.0 x ULN | >3.0 - 5.0 x ULN | >5.0 - 20.0 x ULN | >20.0 x ULN |
| Aspartate Aminotransferase (AST or SGOT) Increased | >ULN - 3.0 x ULN | >3.0 - 5.0 x ULN | >5.0 - 20.0 x ULN | >20.0 x ULN |
| Hyperbilirubinemia *(for endTB protocol versions 1-2)* | >ULN - 1.5 x ULN | >1.5 - 3.0 x ULN | >3.0 - 10.0 x ULN | >10.0 x ULN |