MORE on Relatedness

Devika Singh
and
Sharon Riddler
## Breakdown – as of Oct 15, 2013

<table>
<thead>
<tr>
<th>Severity</th>
<th>NOT Related</th>
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<th>TOTAL</th>
</tr>
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<tbody>
<tr>
<td>Grade 1 – Mild</td>
<td>1,978 (89.3%)</td>
<td>236 (10.7%)</td>
<td>2,214 (56.3%)</td>
</tr>
<tr>
<td>Grade 2 – Mod</td>
<td>1,613 (98.5%)</td>
<td>24 (1.5%)</td>
<td>1,637 (41.6%)</td>
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<tr>
<td>Grade 3 – Severe</td>
<td>66 (98.5%)</td>
<td>1 (1.5%)</td>
<td>67 (1.7%)</td>
</tr>
<tr>
<td>Grade 4 – Potentially Life Threatening</td>
<td>12 (100%)</td>
<td>0</td>
<td>12 (0.3%)</td>
</tr>
<tr>
<td>Grade 5 – Death</td>
<td>1 (100%)</td>
<td>0</td>
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<td><strong>Total</strong></td>
<td>3,670 (93.3%)</td>
<td>261 (6.7%)</td>
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Relationship to Study Product
The site investigator is responsible for assessing the relationship between the AE and the study agent(s).

Site investigators must determine whether there is a reasonable possibility that the study agent(s) caused or contributed to an AE.
Relationship Relies on:

- A temporal relationship between the event and administration of the study agent(s),
- A plausible biological mechanism for the agent to cause the AE,
- Another possible etiology for the AE,
- Previous reports of similar AEs associated with the study agent or other agents in the same class, and
- Recurrence of the AE after re-challenge or resolution after de-challenge, if applicable.
Terms Used:

- **Related** – There is a reasonable possibility that the AE may be related to the study agent(s).

- **Not Related** – There is not a reasonable possibility that the AE is related to the study agent(s).
When Deemed NOT Related:

- An alternative etiology, diagnosis, or explanation for the SAE/AE should be provided.
  
  - If new information becomes available, the relationship assessment of any AE should be reviewed again and updated, as required.

- Explanation may include lack of biologic plausibility
EXAMPLES
Rationale

- Vulvovaginal discomfort:
  - “participant experienced vaginal discomfort with the ring in-situ, which resolved when she removed the ring”
  - “continued symptoms with continued exposure”

- Investigator assessment: RELATED
Genitourinary AEs

- Vulvovaginal discomfort:
  - “participant experienced vaginal discomfort with the ring in-situ, which resolved when she removed the ring”
  - “continued symptoms with continued exposure”

- Investigator assessment: RELATED
Pelvic pain:

“participant had pelvic pain whilst using the ring. The pain resolved when the participant removed the ring.”
Genitourinary AEs

- Pelvic pain:
  - “participant had pelvic pain whilst using the ring. The pain resolved when the participant removed the ring.”
  - Investigator assessment: RELATED
Genitourinary AEs

- Vaginal discharge, participant reported:
  - “infective cause responded to antibiotics”
  - Comments: “treated at local clinic. No tests were done”
Genitourinary AEs

- Vaginal discharge, participant reported:
  - “infective cause responded to antibiotics”
  - Comments: “treated at local clinic. No tests were done”
  - Investigator assessment: NOT RELATED
Systemic AEs

- Pelvic Inflammatory Disease
  - “participant reported that she was treated with an antibiotic, therefore assessed as an infection, this was assessed and treated by a private doctor, hence diagnosis is not known. Symptoms had resolved and pelvic exam was normal.”
Systemic AEs

- Pelvic Inflammatory Disease
  - “participant reported that she was treated with an antibiotic, therefore assessed as an infection, this was assessed and treated by a private doctor, hence diagnosis is not known. Symptoms had resolved and pelvic exam was normal.”

- Investigator assessment: NOT RELATED (due to infection)
Systemic AEs

- Syncope
  - “participant didn't actually faint but had a black veil in front of her eyes, while she was sitting down, and it lasted for a few seconds, and it was only one episode.”
Systemic AEs

- **Syncope**
  - "participant didn't actually faint but had a black veil in front of her eyes, while she was sitting down, and it lasted for a few seconds, and it was only one episode."

- Investigator assessment: RELATED
- PSRT query likely
- Consider: Plausibility? Re-challenge?
Systemic AE

- Abnormal loss of weight: “no other aetiology determined at time of reporting, no endocrine pathology, no loss of appetite, no chronic diarrhoea or vomiting, no history of fasting.”

- Elevated transaminases: “there is a temporal relationship between AE and product use,” “no other cause identified yet”
Systemic AE

- Abnormal loss of weight: “no other aetiology determined at time of reporting, no endocrine pathology, no loss of appetite, no chronic diarrhoea or vomiting, no history of fasting.”

- Elevated transaminases: “there is a temporal relationship between AE and product use,” “no other cause identified yet”

  - Investigator assessment: RELATED
  - PSRT query
  - Consider: Plausibility?
Systemic AE

- Amenorrhea: “no other alternative aetiology. Unlikely to be due to IUCD”
- Elevated transaminases: “there is a temporal relationship between AE and product use,” “no other cause identified yet”
Amenorrhea: “no other alternative aetiology. Unlikely to be due to IUCD”

- Investigator assessment: RELATED
- PSRT query
- Consider: Plausibility? Related to IUD?
Relatedness Summary

- Causality for AE is challenging exercise for investigators
- Focus on the available data considering:
  - Temporal Association with Study Product
  - Dechallenge/Rechallenge
  - Known association (Investigator’s Brochure)
  - Biological Plausibility
  - Other possible Etiology
- Contact PSRT for assistance if needed
EXTRA SLIDES
Related Adverse Events (n=261)

- Meno/metrorrhagia: 48 (18.4%)
- Pelvic pain/uterine pain: 27 (10.3%)
- Vaginal discharge: 27 (10.3%)
- Vulvovaginal discomfort /vulvovaginal pruritus: 27 (10.3%)
- Elevated AST or ALT: 26 (10.0%)
Related Adverse Events (n=261)

- Vaginal odour: 10 (3.8%)
- Neutropenia: 10 (3.8%)
- Headache: 7 (2.7%)
- Vulvovaginitis: 7 (2.7%)
- Cervical erythema: 7 (2.7%)
Related Adverse Events (n=261)

- Cervical discharge or cervicitis: 5 (1.9%)
- Pollakiuria: 5 (1.9%)
- Haemoglobin decreased: 5 (1.9%)
- Coital bleeding: 3 (1.1%)
- Amenorrhea: 3 (1.1%)
- Dysuria: 2 (0.8%)
- Dyspareunia: 2 (0.8%)
- Anemia: 2 (0.8%)
- Abnormal loss of weight: 1 (0.4%)
- Nausea: 1 (0.4%)