MORE on Relatedness

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and

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Breakdown – as of Oct 15, 2013

Severity	NOT Related	Related	TOTAL
Grade 1 – Mild	1,978 (89.3%)	236 (10.7%)	2,214 (56.3%)
Grade 2 – Mod	1,613 (98.5%)	24 (1.5%)	1,637 (41.6%)
Grade 3 – Severe	66 (98.5%)	1 (1.5%)	67 (1.7%)
Grade 4 – Potentially Life Threatening	12 (100%)	0	12 (0.3%%
Grade 5 – Death	1 (100%)	0	1 (0.0%)
	3,670 (93.3%)	**261 (6.7%)**	**3,931 (100%)**

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Relationship to Study Product

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Relationship to Study Agent

- 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

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Genitourinary AEs

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  - Comments: “treated at local clinic. No tests were done”

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  - Comments: "treated at local clinic. No tests were done"
  - Investigator assessment: NOT RELATED

Systemic AEs

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  - “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

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  - 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

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  - “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”

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  - 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”

Systemic AE

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  - 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%)