

001 AE Relationships

Safety MDs

Washington DC

April 23, 2009



Safety MDs perspective

Site	MedDRA	Visit	Severity	Relationship	Regimen	Visit
1	Upper respiratory tract infection	mid oral	Mild	Possibly Related	0/v/0+V	3
1	Upper respiratory tract infection	mid oral	Moderate	Not Related	0/v/0+V	3

Safety MDs perspective

Site	MedDRA	Study Visit	Severity	Relationship	Regimen	Visit
1	Blood creatinine increased	NO DRUG	Mild	Probably not related	v/o+v/o	6
1	Blood creatinine increased	oral start	Mild	Probably not related	v/o/v+o	5
1	Blood creatinine increased	mid vaginal	Mild	Possibly Related	v/o/v+o	3

Safety MDs perspective

Site	MedDRA	Study Visit	Severity	Relationship	Regimen	Visit
2	Hypoglycaemia	mid oral	Mild	Probably not related	o/o+v/v	3
2	Hypoglycaemia	NO DRUG	Mild	Possibly Related	o/o+v/v	10

Safety MDs perspective

Site	MedDRA	Study Visit	Severity	Relationship	Regimen	Visit
1	Hypophosphataemia	mid vaginal	Moderate	Probably Related	v/o/v+o	3
1	Hypophosphataemia	NO DRUG	Mild	Not Related	_	4
1	Hypophosphataemia	mid vaginal	Moderate	Possibly Related	v/o+v/o	3
1	Hypophosphataemia	start oral	Mild	Not Related	o+v/v/o	8

Safety MDs perspective

Site	MedDRA	Study Visit	Severity	Relationship	Regimen	Visit
1	Dermatitis	mid oral	Mild	Possibly Related	0/v/0+V	3
2	Blood calcium decreased	end vaginal	Mild	Possibly Related	o+v/v/o	7
2	Lipoma	end o+v	Mild	Probably not related	o+v/v/o	4



AE relationships to study product

- *Definitely related:* adverse event and administration of study agent are related in time, and a direct association can be demonstrated with the study agent.
- *Probably related:* adverse event and administration of study agent are reasonably related in time, and the adverse event is more likely explained by the study agent than by other causes.
- *Possibly related:* adverse event and administration of study agent are reasonably related in time, and the adverse event can be explained equally well by causes other than the study agent.
- *Probably not related:* a potential relationship between administration of study agent and adverse event could exist, but is unlikely, and the adverse event is most likely explained by causes other than the study agent.
- *Not related:* the adverse event is clearly explained by another cause unrelated to administration of the study agent. Reportable events must have documentation to support the determination of “not related”.



Factors to Consider when Assessing Relationship

- Pre-clinical and clinical profile of the study products: protocol, package inserts, investigators brochures, other published information
- Timing of product use relative to onset, resolution, and/or recurrence of the AE
- Likelihood of observing the AE in the study population in the absence of product use
- Presence of other conditions or exposures that could have caused the AE
- Clinical judgment

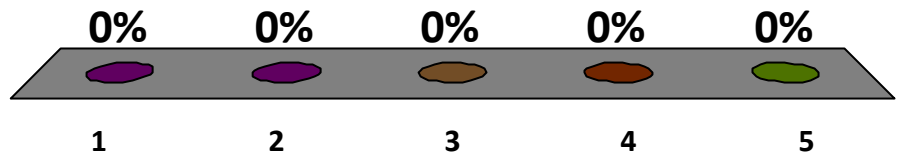


Case 1

- A 24 year old participant is enrolled into MTN 001. At her 3-week visit (mid-study period visit), she is on vaginal product and has a grade 2 hypophosphatemia.

Relationship to study product is:

1. Definitely related
2. Probably related
3. Possibly related
4. Probably not related
5. Definitely not related



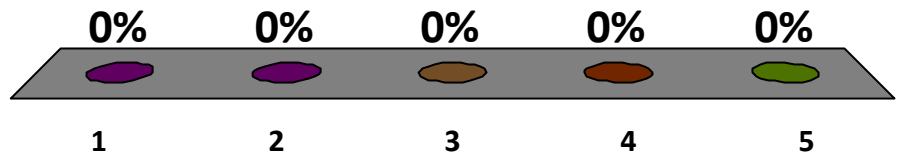


Case 2

- A 26 year old participant is enrolled into 001. At her 3 week visit (mid-study period visit) on combined oral and vaginal product she develops a grade 2 headache.

Relationship to study product is:

1. Definitely related
2. Probably related
3. Possibly related
4. Probably not related
5. Definitely not related



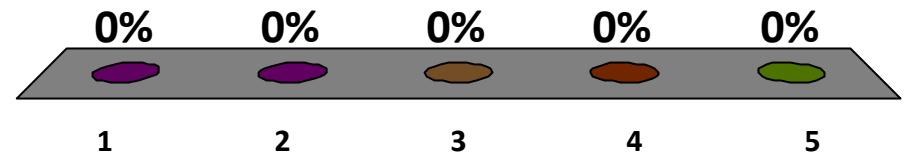


Case 3

- A 26 year old participant is enrolled into 001. At her 10 week visit (mid-study period visit) on combined oral and vaginal product she develops a grade 2 headache. This is her first AE in the study; she had been on oral product during the first study period.

Relationship to study product is:

1. Definitely related
2. Probably related
3. Possibly related
4. Probably not related
5. Definitely not related



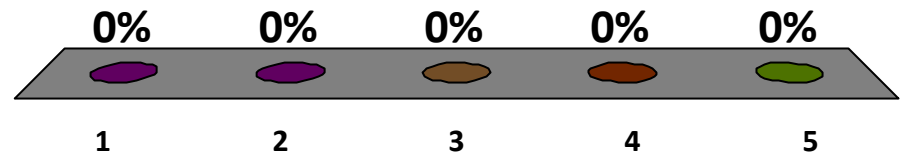


Case 4

- A 26 year old participant is enrolled into 001. At her 14 week visit (study period 3 start) she is beginning vaginal product today. She has just completed a week of off product. She reports a grade 2 headache yesterday. She was last on oral and vaginal product during study period 2 one week ago.

Relationship to study product is:

1. Definitely related
2. Probably related
3. Possibly related
4. Probably not related
5. Definitely not related



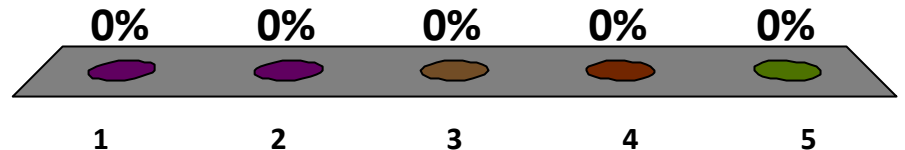


Case 5

- A 26 year old participant is enrolled into 001. She develops a headache after 3 weeks of vaginal product that is exactly the same as she experienced during week 1 of oral product.

Relationship to study product is:

1. Definitely related
2. Probably related
3. Possibly related
4. Probably not related
5. Definitely not related



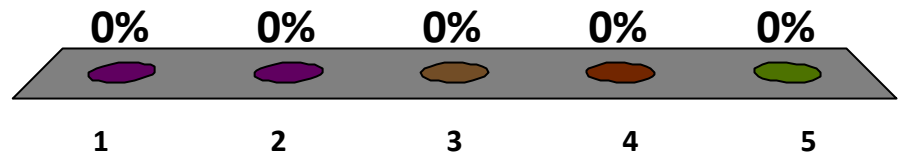


Case 6

- A 25 year old participant is enrolled into 001. She is randomized to receive vaginal product first and develops nausea and headache 3 weeks into study product use. Her routine 3 week visit (mid-study period visit) laboratory evaluation reveals a grade 1 AST elevation.

Relationship to study product is:

1. Definitely related
2. Probably related
3. Possibly related
4. Probably not related
5. Definitely not related



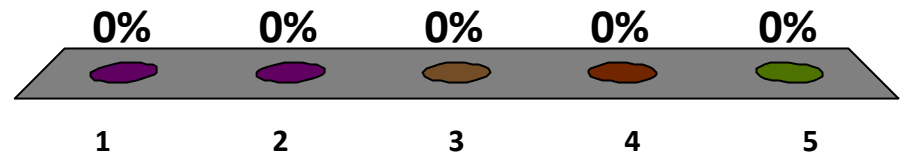


Case 7

- A 25 year old participant is enrolled into 001. Two weeks into oral and vaginal study product she tells the study site that she has been experiencing nausea. The nausea occurs in the morning and lasts for 90 minutes. It has not prevented her from going about her daily activities, and she has had no vomiting.

Relationship to study product is:

1. Definitely related
2. Probably related
3. Possibly related
4. Probably not related
5. Definitely not related



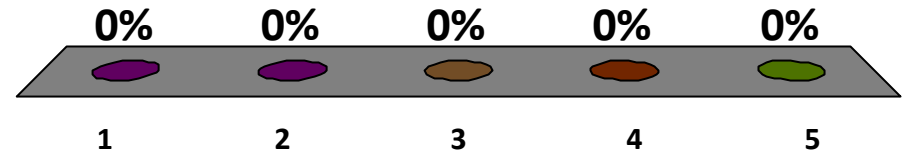


Case 8

- A 34 year old participant is enrolled into 001. She is randomized to receive oral product first. After one week on study product, the participant reports to the study site that she has been experiencing 3 days sore throat, congestion, malaise and arthralgias. These symptoms have not prevented her from going about her daily activities, and she has had no vomiting.

Relationship to study product is:

1. Definitely related
2. Probably related
3. Possibly related
4. Probably not related
5. Definitely not related



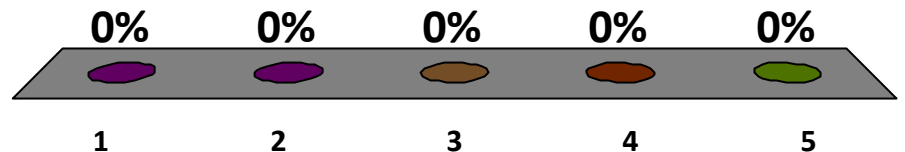


Case 9

- A 28 year old participant is enrolled into 001. She has completed her third week on oral/vaginal product. At her week 3 visit (mid study period visit), she has no complaints. When lab results are obtained, she is found to have grade 1 low calcium.

Relationship to study product

1. Definitely related
2. Probably related
3. Possibly related
4. Probably not related
5. Definitely related



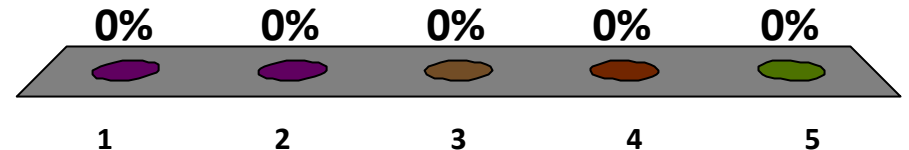


Case 10

- A 21 year old participant is enrolled into 001. At her 3 week visit (mid study period visit) on vaginal product, she has no complaints, but she appears to be a bit tired. When lab results are obtained, she has low phosphorus (grade 2), low magnesium, low calcium and low albumin (all grade 1).

Relationship to study product is:

1. Definitely related
2. Probably related
3. Possibly related
4. Probably not related
5. Definitely not related



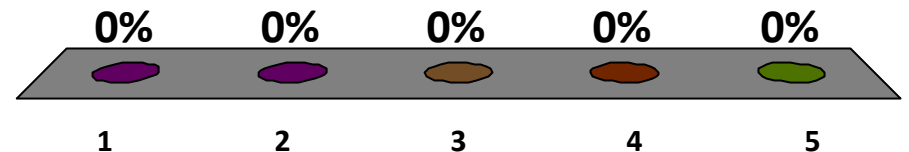


Case 11

- A 21 year old participant is enrolled into 001. She has completed her third week on oral product. On exam, she had no complaints but she appeared to be a bit tired. When lab results were obtained, she had low phosphorus (grade 2), low magnesium, low calcium and low albumin (all grade 1).

Relationship to study product is:

1. Definitely related
2. Probably related
3. Possibly related
4. Probably not related
5. Definitely not related



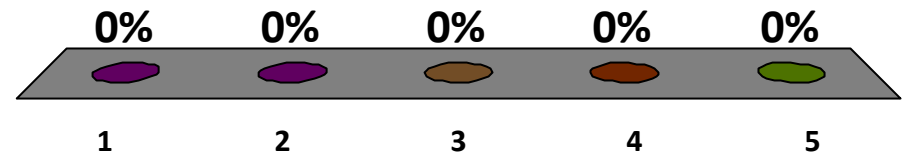


Case 12

- A 26 year old participant is enrolled into 001. She is in the third week following completion of oral product, at this time, she is only on vaginal product, She complains of a three day history of about 3 watery bowel movements per day. She additionally complains of some fatigue, but is otherwise well. Laboratory results were normal.

Relationship to study product is:

1. Definitely related
2. Probably related
3. Possibly related
4. Probably not related
5. Definitely not related





Thank You
