

**Clinical trial results:**

Characterisation of ovulation inhibition and effects on metabolic parameters and haemostatic system of multiple administrations of a fixed-dose combination product containing 0.02 mg ethinylestradiol and 2 mg dienogest (24+4) in a multiple administration, comparative parallel-group trial vs. a marketed product containing 0.02 mg ethinylestradiol and 0.10 mg levonorgestrel with healthy females of childbearing potential

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2012-000041-12 |
| Trial protocol | NL |
| Global end of trial date | 05 March 2013 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 05 August 2016 |
| First version publication date | 05 August 2016 |

Trial information**Trial identification**

| | |
|-----------------------|---------------|
| Sponsor protocol code | 49/11/EDG/TP2 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|--|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | CRO SocraTec R&D study No.: 1259ed11ct |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Zentiva k.s. |
| Sponsor organisation address | U Kabelovny 130, Prague 10 Dolní Měcholupy, Czech Republic, 10237 |
| Public contact | Tomáš Hauser, M.D., Zentiva k.s., 00420 267 243 451, tomas.hauser@sanofi.com |
| Scientific contact | Tomáš Hauser, M.D., Zentiva k.s., 00420 267 243 451, tomas.hauser@sanofi.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 31 May 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 March 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 March 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The aims of this clinical trial are:

- descriptive characterisation of the influence of Test or Reference on ovarian activity determined by means of maximum follicular diameter and Hoogland score
- descriptive characterisation of the effect of Test or Reference on endometrial thickness, cervical mucus as well as on the pituitary and ovarian hormones the latter determined via follicle stimulating hormone (FSH), luteinising hormone (LH), estradiol (E2) and progesterone (P)
- descriptive characterisation of effect of Test or Reference on sex hormone binding globulin (SHBG) and corticosteroid binding globulin (CBG) levels, C-reactive protein, lipid profile as well as haemostatic and carbohydrate parameters
- descriptive characterisation of bleeding pattern
- descriptive characterisation of return of ovulation
- descriptive characterisation of overall safety and tolerability in the study population

Protection of trial subjects:

Subjects we advised to use barrier contraceptive methods.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 28 March 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Netherlands: 60 |
| Worldwide total number of subjects | 60 |
| EEA total number of subjects | 60 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |

| | |
|--|----|
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 60 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

date of first enrolment: 2012-04-16

Clinical site: dinox b.v.

Hanzeplein 1, entrance 53

9713 GZ Groningen,

The Netherlands

Tel.: +31-50-361099-9

Fax: +31-50-361090-9

Pre-assignment

Screening details:

demographic data

medical, gynaecological and obstetric history (prior and concomitant medication, concomitant diseases)

physical examination

gynaecological and breast examination (incl. TVUS)

vital signs, BMI

clinical laboratory: blood analysis incl. haematology and serum chemistry

urine pregnancy test

PAP smear

Period 1

| | |
|------------------------------|----------------------------------|
| Period 1 title | Treatment phase (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

The study was performed in an open design.

Arms

| | |
|------------------------------|------|
| Are arms mutually exclusive? | Yes |
| Arm title | TEST |

Arm description:

Included subjects that entered the treatment phase and received Test treatment, stratified by time point of ovulation observed in the pre-treatment cycle.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BONADEA PLUS |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Once daily administration of one tablet of Test containing 0.02 mg EE and 2 mg DNG over 24 days followed by 4 treatment-free days per cycle. Each treatment was administered over three treatment cycles of 28 days each.

| | |
|------------------|-----------|
| Arm title | REFERENCE |
|------------------|-----------|

Arm description:

Included subjects who entered the treatment phase and received Reference treatment stratified by time point of ovulation observed in the pre-treatment cycle.

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|---------------|
| Investigational medicinal product name | Miranova® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Once daily administration of one tablet of Reference containing 0.02 mg EE and 0.1 mg LNG over 21 days followed by 7 treatment-free days per cycle. Each treatment was administered over three treatment cycles of 28 days each.

| Number of subjects in period 1^[1] | TEST | REFERENCE |
|---|------|-----------|
| Started | 29 | 30 |
| Completed | 27 | 26 |
| Not completed | 2 | 4 |
| Consent withdrawn by subject | 1 | 2 |
| Adverse event, non-fatal | 1 | 1 |
| Protocol deviation | - | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 1 subject not receiving medication:

Reason: drop out due to withdrawal of consent

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | Treatment phase |
|-----------------------|-----------------|

Reporting group description: -

| Reporting group values | Treatment phase | Total | |
|--|-----------------|-------|--|
| Number of subjects | 59 | 59 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 59 | 59 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 24.63 | | |
| standard deviation | ± 3.9 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 59 | 59 | |
| Male | 0 | 0 | |

Subject analysis sets

| | |
|----------------------------|-------------------|
| Subject analysis set title | Full analysis set |
|----------------------------|-------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

The FAS was defined as all subjects of the SAS, who after randomisation, completed at least one treatment cycle of 28 days, or in whom ovulation and/or a Hoogland score >4 were observed in any cycle during randomised treatment.

| | |
|----------------------------|------------------|
| Subject analysis set title | Per protocol set |
|----------------------------|------------------|

| | |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

Subjects:

- who completely passed the pre-defined treatment regimen and
- whose relevant trial variables were available in all periods, and
- who finished the clinical trial without major protocol deviations.

| Reporting group values | Full analysis set | Per protocol set | |
|------------------------|-------------------|------------------|--|
| Number of subjects | 57 | 53 | |

| | | | |
|---|-------|-------|--|
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 57 | 53 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 24.4 | 24.34 | |
| standard deviation | ± 3.7 | ± 3.7 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 57 | 53 | |
| Male | 0 | 0 | |

End points

End points reporting groups

| | |
|---|-------------------|
| Reporting group title | TEST |
| Reporting group description: Included subjects that entered the treatment phase and received Test treatment, stratified by time point of ovulation observed in the pre-treatment cycle. | |
| Reporting group title | REFERENCE |
| Reporting group description: Included subjects who entered the treatment phase and received Reference treatment stratified by time point of ovulation observed in the pre-treatment cycle. | |
| Subject analysis set title | Full analysis set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The FAS was defined as all subjects of the SAS, who after randomisation, completed at least one treatment cycle of 28 days, or in whom ovulation and/or a Hoogland score >4 were observed in any cycle during randomised treatment. | |
| Subject analysis set title | Per protocol set |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Subjects: <ul style="list-style-type: none">• who completely passed the pre-defined treatment regimen and• whose relevant trial variables were available in all periods, and• who finished the clinical trial without major protocol deviations. | |

Primary: Maximum follicular diameter - Treatment cycle 1 (FAS)

| | |
|--|---|
| End point title | Maximum follicular diameter - Treatment cycle 1 (FAS) |
| End point description: | |
| End point type | Primary |
| End point timeframe: Treatment cycle 1, 28 days | |

| End point values | TEST | REFERENCE | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 29 | | |
| Units: mm | | | | |
| arithmetic mean (standard deviation) | 7.14 (± 2.9) | 6.92 (± 1.5) | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Max.follicular diameter-treatment comparison (FAS) |
| Statistical analysis description: The treatment groups were compared per treatment cycle (treatment cycles 1 and 3, only) using a 2-way analysis of variance models, in this case a linear mixed model with repeated measures, including the factors "treatment group", and "time (treatment cycle)" as well as an interaction factor between these two factors. The factor "treatment group" had two levels: Test and Reference. The factor "time" had two levels: treatment cycles 1 and 3. | |

| | |
|---|--------------------------------|
| Comparison groups | TEST v REFERENCE |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[1] |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.9732 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8419 |
| upper limit | 1.1249 |

Notes:

[1] - Several mixed models with different structures of the covariance matrix were calculated to find the best model. The model with best (=smallest) Akaike Information Criteria was to be taken. If more than one Akaike Information Criteria was smallest, the easiest structure of covariance matrix was to be taken; Easiest was compound symmetry, followed by unstructured, autoregressive and autoregressive moving average 1.1.

Primary: Maximum follicular diameter - Treatment cycle 3 (FAS)

| | |
|----------------------------|---|
| End point title | Maximum follicular diameter - Treatment cycle 3 (FAS) |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| Treatment cycle 3, 28 days | |

| End point values | TEST | REFERENCE | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 27 | 26 | | |
| Units: mm | | | | |
| arithmetic mean (standard deviation) | 7 (± 2.44) | 9.1 (± 4.96) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Max.follicular diameter-treatment comparison (FAS) |
| Statistical analysis description: | |
| The treatment groups were compared per treatment cycle (treatment cycles 1 and 3, only) using a 2-way analysis of variance models, in this case a linear mixed model with repeated measures, including the factors "treatment group", and "time (treatment cycle)" as well as an interaction factor between these two factors. The factor "treatment group" had two levels: Test and Reference. The factor "time" had two levels: treatment cycles 1 and 3. | |
| Comparison groups | TEST v REFERENCE |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[2] |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.7479 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6023 |
| upper limit | 0.9287 |

Notes:

[2] - Several mixed models with different structures of the covariance matrix were calculated to find the best model. The model with best (=smallest) Akaike Information Criteria was to be taken. If more than one Akaike Information Criteria was smallest, the easiest structure of covariance matrix was to be taken; Easiest was compound symmetry, followed by unstructured, autoregressive and autoregressive moving average 1.1.

Primary: Hoogland and Skouby score - Treatment cycle 1 (FAS)

| | |
|-----------------|---|
| End point title | Hoogland and Skouby score - Treatment cycle 1 (FAS) |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Treatment cycle 1, 28 days

| End point values | TEST | REFERENCE | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 29 | | |
| Units: cumulative count | 39 | 34 | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Hoogland/Skouby score-treatment comparison (FAS) |
|----------------------------|--|

Statistical analysis description:

For the maximum Hoogland and Skouby score, the treatment groups will be compared per treatment cycle (treatment cycle 1 and 3) using the two-sided Mann-Whitney-U Test.

| | |
|---|-------------------------|
| Comparison groups | REFERENCE v TEST |
| Number of subjects included in analysis | 57 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | > 0.05 |
| Method | Wilcoxon (Mann-Whitney) |

Primary: Hoogland and Skouby score - Treatment cycle 3 (FAS)

| | |
|-----------------|---|
| End point title | Hoogland and Skouby score - Treatment cycle 3 (FAS) |
|-----------------|---|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Treatment cycle 3, 28 days

| End point values | TEST | REFERENCE | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 27 | 26 | | |
| Units: cumulative count | 38 | 49 | | |

Statistical analyses

| Statistical analysis title | Hoogland/Skouby score-Treatment comparison (FAS) |
|---|--|
| Statistical analysis description: | |
| For the maximum Hoogland and Skouby score, the treatment groups will be compared per treatment cycle (treatment cycle 1 and 3) using the two-sided Mann-Whitney-U Test. | |
| Comparison groups | TEST v REFERENCE |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.05 |
| Method | Wilcoxon (Mann-Whitney) |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

125 study days - Treatment phase (3 Treatment cycles of 28 days) + Follow up phase

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------|
| Reporting group title | TEST |
|-----------------------|------|

Reporting group description:

Adverse events reported by subjects that received the Test treatment

| | |
|-----------------------|-----------|
| Reporting group title | REFERENCE |
|-----------------------|-----------|

Reporting group description:

Adverse events reported by subjects that received the Reference treatment

| Serious adverse events | TEST | REFERENCE | |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 30 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | TEST | REFERENCE | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 28 / 29 (96.55%) | 29 / 30 (96.67%) | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| General disorders and administration site conditions | | | |
| Influenza like illness | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 30 (3.33%) | |
| occurrences (all) | 2 | 1 | |
| Malaise | | | |

| | | | |
|---|----------------------|-----------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 0 / 30 (0.00%) 0 | |
| Hangover subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 4 | 1 / 30 (3.33%) 1 | |
| Irritability subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 2 | |
| Reproductive system and breast disorders | | | |
| Breast tenderness subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 2 / 30 (6.67%) 2 | |
| Dysmenorrhoea subjects affected / exposed occurrences (all) | 5 / 29 (17.24%) 9 | 8 / 30 (26.67%) 12 | |
| Breast pain subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 3 | 1 / 30 (3.33%) 1 | |
| Vaginal discharge subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Vulvovaginal pruritus subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Coital bleeding subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 2 / 30 (6.67%) 2 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 2 / 30 (6.67%) 2 | |
| Cough | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Psychiatric disorders | | | |
| Libido decreased | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Affect lability | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Traumatic haematoma | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Contusion | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 30 (3.33%) | |
| occurrences (all) | 2 | 1 | |
| Concussion | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eye injury | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 12 / 29 (41.38%) | 17 / 30 (56.67%) | |
| occurrences (all) | 28 | 24 | |

| | | | |
|--|---|--|--|
| Migraine subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 30 (0.00%) 0 | |
| Dizziness subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 0 / 30 (0.00%) 0 | |
| Amnesia subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 30 (0.00%) 0 | |
| Migraine with aura subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 1 / 30 (3.33%) 1 | |
| Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 1 / 30 (3.33%) 1 | |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Eye disorders Conjunctivitis subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain lower subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 3 7 / 29 (24.14%) 8 5 / 29 (17.24%) 6 1 / 29 (3.45%) 1 | 0 / 30 (0.00%) 0 5 / 30 (16.67%) 7 3 / 30 (10.00%) 3 0 / 30 (0.00%) 0 | |

| | | | |
|--|----------------|-----------------|--|
| Abdominal distension | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 30 (6.67%) | |
| occurrences (all) | 2 | 3 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| Anorectal discomfort | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lip swelling | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Dental discomfort | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Toothache | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Acne | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 4 / 30 (13.33%) | |
| occurrences (all) | 2 | 4 | |
| Eczema | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Renal and urinary disorders | | | |

| | | | |
|--|------------------------|------------------------|--|
| Dysuria subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 0 / 30 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 3 | 0 / 30 (0.00%) 0 | |
| Arthralgia subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 2 / 30 (6.67%) 2 | |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 10 / 29 (34.48%) 10 | 15 / 30 (50.00%) 19 | |
| Gastroenteritis subjects affected / exposed occurrences (all) | 8 / 29 (27.59%) 8 | 2 / 30 (6.67%) 2 | |
| Oral herpes subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 1 / 30 (3.33%) 1 | |
| Influenza subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 5 / 30 (16.67%) 5 | |
| Cystitis subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 2 / 30 (6.67%) 2 | |
| Furuncle subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Carbuncle subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 1 / 30 (3.33%) 1 | |
| Vulvovaginal candidiasis subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 2 / 30 (6.67%) 2 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|--|---------------------|---------------------|--|
| Increased appetite subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 30 (0.00%) 0 | |
|--|---------------------|---------------------|--|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported