

**Clinical trial results:**

A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Five-Treatment, Four 6-Week Period Cross-Over, Multi-Center Study to Evaluate the Effect of Adding GSK2190915 100mg, GSK2190915 300mg, Montelukast 10mg or Placebo Tablets Once Daily or Salmeterol 50mcg Inhalation Powder Twice Daily to Fluticasone Propionate 100mcg Inhalation Powder Twice Daily in Uncontrolled Asthmatic Subjects ≥ 12 Years of Age

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2010-019466-81 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 25 October 2011 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 29 December 2016 |
| First version publication date | 29 December 2016 |

Trial information**Trial identification**

| | |
|-----------------------|--------|
| Sponsor protocol code | 114255 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | GlaxoSmithKline |
| Sponsor organisation address | 980 Great West Road, Brentford, Middlesex, United Kingdom, |
| Public contact | GSK Response Center, GlaxoSmithKline, 1 866-435-7343, |
| Scientific contact | GSK Response Center, GlaxoSmithKline, 1 866-435-7343, |

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? | Yes |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 14 December 2011 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 October 2011 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

to evaluate the efficacy and safety of adding GSK2190915 100mg, GSK2190915 300mg or placebo tablets administered once daily to FP 100mcg inhalation administered twice daily in uncontrolled asthmatic female subjects ≥ 12 years of age over the course of 6 weeks treatment.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 06 September 2010 |
| 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 | United States: 341 |
| Worldwide total number of subjects | 341 |
| EEA total number of subjects | 0 |

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) | 41 |
| Adults (18-64 years) | 290 |
| From 65 to 84 years | 10 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 341 participants (par.) were screened, and 162 participants were randomized. A protocol amendment necessitated withdrawal of all male participants and further enrollment of female participants only.

Pre-assignment

Screening details:

Par. meeting screening criteria, self-administered open-label fluticasone propionate 100 micrograms (μg) twice daily for 14-28 days. Eligible par. were assigned to 1 of 10 treatment sequences, receiving 4 of 5 double-blind treatments. Par. aged 12-14 years did not receive montelukast. Rescue medication (albuterol inhalation) was provided.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Subject |

Arms

| | |
|-----------|-------------------------|
| Arm title | All Treatments Combined |
|-----------|-------------------------|

Arm description:

In a total of 4 treatment periods (each of 6 weeks - the first 3 weeks considered as active washout), participants received 4 of the 5 possible treatments (A/B/C/D/E) in a double-blind double-dummy, cross-over manner. Fluticasone propionate (FP) 100 μg oral inhalation was a part of each treatment. Added regimen were, A: GSK2190915 100 milligrams (mg) once daily (OD), B: GSK2190915 300 mg OD, C: montelukast 10 mg OD, D: placebo twice daily (BID), E: salmeterol 50 μg and placebo BID. Albuterol aerosol was provided as a rescue inhalation.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Fluticasone Propionate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Oral use |

Dosage and administration details:

One inhalation of fluticasone propionate 100 μg BID for 6 weeks

| | |
|--|-------------------|
| Investigational medicinal product name | GSK2190915 100 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

One tablet of GSK2190915 100 mg every morning for 6 weeks

| | |
|--|-----------------------------------|
| Investigational medicinal product name | Fluticasone Propionate/Salmeterol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Oral use |

Dosage and administration details:

One inhalation of fluticasone propionate/salmeterol 100 μg /50 μg BID for 6 weeks

| | |
|--|------------------------------|
| Investigational medicinal product name | GSK2190915 200 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| One tablet of GSK2190915 200 mg every morning for 6 weeks | |
| Investigational medicinal product name | Placebo to match GSK2190915 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Two tablets every morning for 6 weeks | |
| Investigational medicinal product name | Montelukast |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| One capsule of montelukast 10 mg every evening for 6 weeks | |
| Investigational medicinal product name | Placebo to match Montelukast |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| One capsule every evening for 6 weeks | |

| Number of subjects in period 1^[1] | All Treatments Combined |
|---|--------------------------------|
| Started | 162 |
| Completed | 93 |
| Not completed | 69 |
| Physician decision | 3 |
| Consent withdrawn by subject | 9 |
| Adverse event, non-fatal | 1 |
| other Sponsor Decision (Protocol Amendme | 11 |
| Lost to follow-up | 3 |
| Lack of efficacy | 36 |
| Protocol deviation | 6 |

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: A total of 341 participants were screened and 162 participants were randomized.

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | All Treatments Combined |
|-----------------------|-------------------------|

Reporting group description:

In a total of 4 treatment periods (each of 6 weeks - the first 3 weeks considered as active washout), participants received 4 of the 5 possible treatments (A/B/C/D/E) in a double-blind double-dummy, cross-over manner. Fluticasone propionate (FP) 100 µg oral inhalation was a part of each treatment. Added regimen were, A: GSK2190915 100 milligrams (mg) once daily (OD), B: GSK2190915 300 mg OD, C: montelukast 10 mg OD, D: placebo twice daily (BID), E: salmeterol 50 µg and placebo BID. Albuterol aerosol was provided as a rescue inhalation.

| Reporting group values | All Treatments Combined | Total | |
|---|-------------------------|-------|--|
| Number of subjects | 162 | 162 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Age continuous description | | | |
| Units: years | | | |
| arithmetic mean | 36.8 | | |
| standard deviation | ± 14.43 | - | |
| Gender categorical | | | |
| Gender categorical description | | | |
| Units: Subjects | | | |
| Female | 151 | 151 | |
| Male | 11 | 11 | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| African American/African Heritage | 42 | 42 | |
| American Indian or Alaska Native | 1 | 1 | |
| Asian - Central/South Asian Heritage | 1 | 1 | |
| White - White/Caucasian/European Heritage | 115 | 115 | |
| Mixed Race | 2 | 2 | |
| Missing | 1 | 1 | |

End points

End points reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | All Treatments Combined |
|-----------------------|-------------------------|

Reporting group description:

In a total of 4 treatment periods (each of 6 weeks - the first 3 weeks considered as active washout), participants received 4 of the 5 possible treatments (A/B/C/D/E) in a double-blind double-dummy, cross-over manner. Fluticasone propionate (FP) 100 µg oral inhalation was a part of each treatment. Added regimen were, A: GSK2190915 100 milligrams (mg) once daily (OD), B: GSK2190915 300 mg OD, C: montelukast 10 mg OD, D: placebo twice daily (BID), E: salmeterol 50 µg and placebo BID. Albuterol aerosol was provided as a rescue inhalation.

| | |
|----------------------------|--------------|
| Subject analysis set title | FP + Placebo |
|----------------------------|--------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Participants received FP 100 µg oral inhalation twice daily (BID) for 6 weeks (first 3 weeks considered as active washout), in one of the 4 treatment periods. Placebo administered every morning (AM) was added to the dosing regimen. Blinding was maintained by administration of a montelukast-matching placebo capsule every evening (PM). Albuterol aerosol was provided as a rescue inhalation.

| | |
|----------------------------|------------------------|
| Subject analysis set title | FP + GSK2190915 100 mg |
|----------------------------|------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Participants received FP 100 µg oral inhalation BID for 6 weeks (first 3 weeks considered as active washout), in one of the 4 treatment periods. GSK2190915 100 mg AM was added to the dosing regimen. Blinding was maintained by PM administration of a montelukast-matching placebo capsule. Albuterol aerosol was provided as a rescue inhalation.

| | |
|----------------------------|------------------------|
| Subject analysis set title | FP + GSK2190915 300 mg |
|----------------------------|------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Participants received FP 100 µg oral inhalation BID for 6 weeks (first 3 weeks considered as active washout), in one of the 4 treatment periods. GSK2190915 300 mg AM was added to the dosing regimen. Blinding was maintained by PM administration of a montelukast-matching placebo capsule. Albuterol aerosol was provided as a rescue inhalation.

| | |
|----------------------------|------------------|
| Subject analysis set title | FP + Montelukast |
|----------------------------|------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Participants received FP 100 µg oral inhalation BID for 6 weeks (first 3 weeks considered as active washout), in one of the 4 treatment periods. Montelukast 10 mg capsule administered PM was added to the dosing regimen. Blinding was maintained by AM administration of GSK2190915-matching placebo tablets. Albuterol aerosol was provided as a rescue inhalation.

| | |
|----------------------------|-----------------|
| Subject analysis set title | FP / Salmeterol |
|----------------------------|-----------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Participants received a combination of FP 100 µg and salmeterol 50 µg oral inhalation BID for 6 weeks (first 3 weeks considered as active washout), in one of the 4 treatment periods. Blinding was maintained by AM administration of GSK2190915-matching placebo tablets and PM administration of a montelukast-matching placebo capsule. Albuterol aerosol was provided as a rescue inhalation.

Primary: Trough (AM pre-dose and pre-rescue bronchodilator) forced expiratory volume in 1 second (FEV1) at the end of the 6-week treatment period

| | |
|-----------------|--|
| End point title | Trough (AM pre-dose and pre-rescue bronchodilator) forced expiratory volume in 1 second (FEV1) at the end of the 6-week treatment period |
|-----------------|--|

End point description:

FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. FEV1 was measured electronically using spirometry, prior to study medication and any rescue albuterol (bronchodilator) use. At the end of the 6-week treatment period, FEV1 was measured approximately 24 hours after the participant's last morning dose of study medication and approximately 12 hours after the evening dose of study medication. Trough FEV1 was analyzed using

mixed effect analysis of covariance (ANCOVA) model for treatment effects, incorporating fixed effects of baseline, period, age, center, smoking status, and random effect of participant. Intent-to-Treat Population (ITT) is defined as all participants who were randomized and received at least one dose of study drug.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| End of Week 6 | |

| End point values | FP + Placebo | FP + GSK2190915 100 mg | FP + GSK2190915 300 mg | FP + Montelukast |
|-------------------------------------|----------------------|------------------------|------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 92 ^[1] | 92 ^[2] | 93 ^[3] | 94 ^[4] |
| Units: Liters (L) | | | | |
| least squares mean (standard error) | 2.36 (± 0.03) | 2.39 (± 0.03) | 2.4 (± 0.03) | 2.42 (± 0.03) |

Notes:

- [1] - ITT Population
- [2] - ITT Population
- [3] - ITT Population
- [4] - ITT Population

| End point values | FP / Salmeterol | | | |
|-------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 93 ^[5] | | | |
| Units: Liters (L) | | | | |
| least squares mean (standard error) | 2.43 (± 0.03) | | | |

Notes:

- [5] - ITT Population

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---------------------------------------|
| Comparison groups | FP + GSK2190915 100 mg v FP + Placebo |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.268 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.026 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02 |
| upper limit | 0.07 |

| Statistical analysis title | Statistical analysis 2 |
|-----------------------------------|------------------------|
|-----------------------------------|------------------------|

| | |
|---|---------------------------------------|
| Comparison groups | FP + Placebo v FP + GSK2190915 300 mg |
| Number of subjects included in analysis | 185 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.08 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.042 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 0.09 |

| | |
|---|---------------------------------|
| Statistical analysis title | Statistical analysis 3 |
| Comparison groups | FP + Placebo v FP + Montelukast |
| Number of subjects included in analysis | 186 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.017 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.056 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.01 |
| upper limit | 0.1 |

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 4 |
| Comparison groups | FP + Placebo v FP / Salmeterol |
| Number of subjects included in analysis | 185 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.002 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.074 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.03 |
| upper limit | 0.12 |

Secondary: Daily trough (morning pre-dose and pre-rescue bronchodilator) morning peak expiratory flow (PEF) averaged over the last 3 weeks of the 6-week treatment period

| | |
|-----------------|--|
| End point title | Daily trough (morning pre-dose and pre-rescue bronchodilator) morning peak expiratory flow (PEF) averaged over the last 3 weeks of the 6-week treatment period |
|-----------------|--|

End point description:

The PEF is a measure of lung function and measures how fast a person can breathe out. Trough PEF was measured every morning prior to study medication dose and any rescue albuterol (bronchodilator) use. Participants recorded PEF in a daily electronic diary (eDiary). Daily trough morning PEF was averaged over the last 3 weeks of the 6-week treatment period, and analyzed using mixed effect ANCOVA model for treatment effects, incorporating fixed effects of baseline, period, age, center, smoking status, and random effects of participant.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 4 to Week 6

| End point values | FP + Placebo | FP + GSK2190915 100 mg | FP + GSK2190915 300 mg | FP + Montelukast |
|-------------------------------------|----------------------|------------------------|------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 92 ^[6] | 92 ^[7] | 92 ^[8] | 93 ^[9] |
| Units: Liters/minute (L/min) | | | | |
| least squares mean (standard error) | 349.19 (± 4.08) | 350.14 (± 4.06) | 354.96 (± 4.07) | 354.17 (± 4.05) |

Notes:

[6] - ITT Population

[7] - ITT Population

[8] - ITT Population

[9] - ITT Population

| End point values | FP / Salmeterol | | | |
|-------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 95 ^[10] | | | |
| Units: Liters/minute (L/min) | | | | |
| least squares mean (standard error) | 361.33 (± 4.05) | | | |

Notes:

[10] - ITT Population

Statistical analyses

| | |
|---|---------------------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | FP + Placebo v FP + GSK2190915 100 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.751 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.946 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.91 |
| upper limit | 6.81 |

| | |
|---|---------------------------------------|
| Statistical analysis title | Statistical analysis 2 |
| Comparison groups | FP + Placebo v FP + GSK2190915 300 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.049 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 5.771 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.03 |
| upper limit | 11.51 |

| | |
|---|---------------------------------|
| Statistical analysis title | Statistical analysis 3 |
| Comparison groups | FP + Placebo v FP + Montelukast |
| Number of subjects included in analysis | 185 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.123 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 4.983 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.35 |
| upper limit | 11.32 |

| | |
|-----------------------------------|--------------------------------|
| Statistical analysis title | Statistical analysis 4 |
| Comparison groups | FP + Placebo v FP / Salmeterol |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 187 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 12.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.93 |
| upper limit | 18.35 |

Secondary: Daily evening PEF averaged over the last 3 weeks of the 6-week treatment period

| | |
|-----------------|---|
| End point title | Daily evening PEF averaged over the last 3 weeks of the 6-week treatment period |
|-----------------|---|

End point description:

The PEF is a measure of lung function and measures how fast a person can breathe out. PEF was measured every evening prior to study medication dose and any rescue albuterol (bronchodilator) use. Participants recorded PEF in a daily eDiary. Daily evening PEF was averaged over the last 3 weeks of the 6-week treatment period, and analyzed using mixed effect ANCOVA model for treatment effects, incorporating fixed effects of baseline, period, age, center, smoking status, and random effects of participant.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 4 to Week 6

| End point values | FP + Placebo | FP + GSK2190915 100 mg | FP + GSK2190915 300 mg | FP + Montelukast |
|-------------------------------------|----------------------|------------------------|------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 92 ^[11] | 92 ^[12] | 92 ^[13] | 93 ^[14] |
| Units: L/min | | | | |
| least squares mean (standard error) | 354.06 (± 4.03) | 355.71 (± 4.02) | 359.16 (± 4.03) | 358.88 (± 4.01) |

Notes:

[11] - ITT Population

[12] - ITT Population

[13] - ITT Population

[14] - ITT Population

| End point values | FP / Salmeterol | | | |
|-------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 95 ^[15] | | | |
| Units: L/min | | | | |
| least squares mean (standard error) | 364.35 (± 4) | | | |

Notes:

[15] - ITT Population

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---------------------------------------|
| Comparison groups | FP + Placebo v FP + GSK2190915 100 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.563 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.651 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.97 |
| upper limit | 7.27 |

| Statistical analysis title | Statistical analysis 2 |
|---|---------------------------------------|
| Comparison groups | FP + Placebo v FP + GSK2190915 300 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.072 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 5.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.47 |
| upper limit | 10.67 |

| Statistical analysis title | Statistical analysis 3 |
|-----------------------------------|---------------------------------|
| Comparison groups | FP + Placebo v FP + Montelukast |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 185 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.126 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 4.822 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.37 |
| upper limit | 11.02 |

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 4 |
| Comparison groups | FP + Placebo v FP / Salmeterol |
| Number of subjects included in analysis | 187 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 10.292 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.21 |
| upper limit | 16.38 |

Secondary: Daily (average of morning and evening) PEF averaged over the last 3 weeks of the 6 -week treatment period between GSK2190915 and montelukast groups

| | |
|-----------------|---|
| End point title | Daily (average of morning and evening) PEF averaged over the last 3 weeks of the 6 -week treatment period between GSK2190915 and montelukast groups |
|-----------------|---|

End point description:

The PEF is a measure of lung function and measures how fast a person can breathe out. PEF was measured every morning and evening prior to study medication dose and any rescue albuterol (bronchodilator) use. Participants recorded PEF in a daily eDiary. Daily average of morning and evening PEF was averaged over the last 3 weeks of the 6-week treatment period, and analyzed using mixed effect ANCOVA model for treatment effects, incorporating fixed effects of baseline, period, age, center, smoking status, and random effects of participant. This outcome measure explored the efficacy between GSK2190915 and montelukast due to the dosing time difference.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 4 to Week 6

| End point values | FP + GSK2190915 100 mg | FP + GSK2190915 300 mg | FP + Montelukast | |
|-------------------------------------|------------------------|------------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 93 ^[16] | 92 ^[17] | 93 ^[18] | |
| Units: L/min | | | | |
| least squares mean (standard error) | 352.37 (± 3.9) | 356.16 (± 3.91) | 356.52 (± 3.9) | |

Notes:

[16] - ITT Population

[17] - ITT Population

[18] - ITT Population

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---|
| Comparison groups | FP + GSK2190915 100 mg v FP + Montelukast |
| Number of subjects included in analysis | 186 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -4.154 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.36 |
| upper limit | 1.06 |

| Statistical analysis title | Statistical analysis 2 |
|---|---|
| Comparison groups | FP + GSK2190915 300 mg v FP + Montelukast |
| Number of subjects included in analysis | 185 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.364 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.22 |
| upper limit | 5.5 |

Secondary: Daily asthma symptom score averaged over the last 3 weeks of the 6-week treatment period

| | |
|-----------------|--|
| End point title | Daily asthma symptom score averaged over the last 3 weeks of the 6-week treatment period |
|-----------------|--|

End point description:

Daytime and night time asthma symptoms were recorded every evening at bedtime and every morning upon rising, respectively, before taking any rescue or study medication and before assessing the PEF. Symptoms were recorded on scales ranging from '0' (implying no symptoms) to either 5 (for daytime

symptoms) or 4 (for night time symptoms) (implying severe symptoms). Participants recorded the symptoms in a daily eDiary. 24-hour period asthma symptom scores were averaged over the last 3 weeks of the 6-week treatment period, and analyzed using mixed effect ANCOVA model for treatment effects, incorporating fixed effects of baseline, period, age, center, smoking status, and random effects of participant.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 4 to Week 6 | |

| End point values | FP + Placebo | FP + GSK2190915 100 mg | FP + GSK2190915 300 mg | FP + Montelukast |
|-------------------------------------|----------------------|------------------------|------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 92 ^[19] | 90 ^[20] | 92 ^[21] | 93 ^[22] |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | 2.26 (± 0.12) | 2.26 (± 0.12) | 2.15 (± 0.12) | 2.22 (± 0.12) |

Notes:

[19] - ITT Population

[20] - ITT Population

[21] - ITT Population

[22] - ITT Population

| End point values | FP / Salmeterol | | | |
|-------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 95 ^[23] | | | |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | 2.25 (± 0.12) | | | |

Notes:

[23] - ITT Population

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---------------------------------------|
| Comparison groups | FP + Placebo v FP + GSK2190915 100 mg |
| Number of subjects included in analysis | 182 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.957 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.005 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.18 |
| upper limit | 0.17 |

| | |
|---|---------------------------------------|
| Statistical analysis title | Statistical analysis 2 |
| Comparison groups | FP + Placebo v FP + GSK2190915 300 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.213 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.108 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.28 |
| upper limit | 0.06 |

| | |
|---|---------------------------------|
| Statistical analysis title | Statistical analysis 3 |
| Comparison groups | FP + Placebo v FP + Montelukast |
| Number of subjects included in analysis | 185 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.647 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.038 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.2 |
| upper limit | 0.12 |

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 4 |
| Comparison groups | FP + Placebo v FP / Salmeterol |
| Number of subjects included in analysis | 187 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.894 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.011 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.17 |
| upper limit | 0.15 |

Secondary: Daily rescue short-acting beta2-agonist (SABA) use averaged over the last 3 weeks of the 6-week treatment period

| | |
|-----------------|--|
| End point title | Daily rescue short-acting beta2-agonist (SABA) use averaged over the last 3 weeks of the 6-week treatment period |
|-----------------|--|

End point description:

A SABA (albuterol) was provided to participants as a rescue medication, to use as needed for symptomatic relief of asthma symptoms. Participants were required to record their albuterol use in the morning and in the evening. Participants recorded the number of inhalations of rescue medication in a daily eDiary. The daily rescue SABA use was averaged over the last 3 weeks of the 6-week treatment period, and analyzed using mixed effect ANCOVA model for treatment effects, incorporating fixed effects of baseline, period, age, center, smoking status, and random effects of participant.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 4 to Week 6

| End point values | FP + Placebo | FP + GSK2190915 100 mg | FP + GSK2190915 300 mg | FP + Montelukast |
|-------------------------------------|----------------------|------------------------|------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 92 ^[24] | 90 ^[25] | 92 ^[26] | 93 ^[27] |
| Units: Number of inhalations | | | | |
| least squares mean (standard error) | 2.17 (± 0.13) | 2.14 (± 0.13) | 2.03 (± 0.13) | 2.09 (± 0.13) |

Notes:

[24] - ITT Population

[25] - ITT Population

[26] - ITT Population

[27] - ITT Population

| End point values | FP / Salmeterol | | | |
|-------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 95 ^[28] | | | |
| Units: Number of inhalations | | | | |
| least squares mean (standard error) | 2.08 (± 0.13) | | | |

Notes:

[28] - ITT Population

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---------------------------------------|
| Comparison groups | FP + Placebo v FP + GSK2190915 100 mg |
| Number of subjects included in analysis | 182 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.811 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.025 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.23 |
| upper limit | 0.18 |

| | |
|---|---------------------------------------|
| Statistical analysis title | Statistical analysis 2 |
| Comparison groups | FP + Placebo v FP + GSK2190915 300 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.2 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.133 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.34 |
| upper limit | 0.07 |

| | |
|---|---------------------------------|
| Statistical analysis title | Statistical analysis 3 |
| Comparison groups | FP + Placebo v FP + Montelukast |
| Number of subjects included in analysis | 185 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.415 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.076 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.26 |
| upper limit | 0.11 |

| | |
|-----------------------------------|--------------------------------|
| Statistical analysis title | Statistical analysis 4 |
| Comparison groups | FP + Placebo v FP / Salmeterol |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 187 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.358 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.084 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.26 |
| upper limit | 0.1 |

Secondary: Percentage of symptom-free days during the last 3 weeks of the 6-week treatment period

| | |
|-----------------|--|
| End point title | Percentage of symptom-free days during the last 3 weeks of the 6-week treatment period |
|-----------------|--|

End point description:

Daytime asthma symptoms were recorded every evening at bedtime, before taking any rescue or study medication and before assessing the PEF. Symptoms were recorded on a 6-point scale ranging from '0' (implying no symptoms) to 5 (implying severe symptoms). Participants recorded the symptoms in a daily eDiary. The number of days when symptoms were not experienced ("symptom-free days") during the last 3 weeks of the 6-week treatment period were counted, and percentage calculated by dividing by 21 and multiplying by 100. Analysis was done using mixed effect ANCOVA model for treatment effects, incorporating fixed effects of baseline, period, age, center, smoking status, and random effects of participant.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 4 to Week 6

| End point values | FP + Placebo | FP + GSK2190915 100 mg | FP + GSK2190915 300 mg | FP + Montelukast |
|-------------------------------------|----------------------|------------------------|------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 92 ^[29] | 92 ^[30] | 92 ^[31] | 93 ^[32] |
| Units: Percentage of days | | | | |
| least squares mean (standard error) | 30.84 (± 3.04) | 33.51 (± 3.02) | 36.14 (± 3.03) | 34.88 (± 3.01) |

Notes:

[29] - ITT Population

[30] - ITT Population

[31] - ITT Population

[32] - ITT Population

| End point values | FP / Salmeterol | | | |
|-------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 95 ^[33] | | | |
| Units: Percentage of days | | | | |
| least squares mean (standard error) | 35.45 (± 3.02) | | | |

Notes:

[33] - ITT Population

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---------------------------------------|
| Comparison groups | FP + Placebo v FP + GSK2190915 100 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.285 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.666 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.24 |
| upper limit | 7.57 |

| Statistical analysis title | Statistical analysis 2 |
|---|---------------------------------------|
| Comparison groups | FP + Placebo v FP + GSK2190915 300 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.035 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 5.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.38 |
| upper limit | 10.22 |

| Statistical analysis title | Statistical analysis 3 |
|-----------------------------------|---------------------------------|
| Comparison groups | FP + Placebo v FP + Montelukast |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 185 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.09 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 4.036 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.63 |
| upper limit | 8.7 |

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 4 |
| Comparison groups | FP + Placebo v FP / Salmeterol |
| Number of subjects included in analysis | 187 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.047 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 4.602 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.06 |
| upper limit | 9.14 |

Secondary: Percentage of symptom-free nights during the last 3 weeks of the 6 week treatment period

| | |
|---|--|
| End point title | Percentage of symptom-free nights during the last 3 weeks of the 6 week treatment period |
| End point description: | |
| <p>Night time asthma symptoms were recorded every morning upon rising, before taking any rescue or study medication and before assessing the PEF. Symptoms were recorded on a 5-point scale ranging from '0' (implying no symptoms) to 4 (implying severe symptoms). Participants recorded the symptoms in a daily eDiary. The number of nights when symptoms were not experienced ("symptom-free nights") during the last 3 weeks of the 6-week treatment period were counted, and percentage calculated by dividing by 21 and multiplying by 100. Analysis was done using mixed effect ANCOVA model for treatment effects, incorporating fixed effects of baseline, period, age, center, smoking status, and random effects of participant.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Week 4 to Week 6 | |

| End point values | FP + Placebo | FP + GSK2190915 100 mg | FP + GSK2190915 300 mg | FP + Montelukast |
|-------------------------------------|----------------------|------------------------|------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 92 ^[34] | 92 ^[35] | 92 ^[36] | 93 ^[37] |
| Units: Percentage of nights | | | | |
| least squares mean (standard error) | 37.21 (± 2.87) | 38.22 (± 2.85) | 40.55 (± 2.85) | 37.7 (± 2.84) |

Notes:

[34] - ITT Population

[35] - ITT Population

[36] - ITT Population

[37] - ITT Population

| End point values | FP / Salmeterol | | | |
|-------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 95 ^[38] | | | |
| Units: Percentage of nights | | | | |
| least squares mean (standard error) | 38.47 (± 2.85) | | | |

Notes:

[38] - ITT Population

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---------------------------------------|
| Comparison groups | FP + Placebo v FP + GSK2190915 100 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.668 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.014 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.64 |
| upper limit | 5.67 |

| Statistical analysis title | Statistical analysis 2 |
|---|---------------------------------------|
| Comparison groups | FP + Placebo v FP + GSK2190915 300 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.156 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 3.349 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.29 |
| upper limit | 7.98 |

| | |
|---|---------------------------------|
| Statistical analysis title | Statistical analysis 3 |
| Comparison groups | FP + Placebo v FP + Montelukast |
| Number of subjects included in analysis | 185 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.822 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.496 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.83 |
| upper limit | 4.82 |

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 4 |
| Comparison groups | FP + Placebo v FP / Salmeterol |
| Number of subjects included in analysis | 187 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.555 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.94 |
| upper limit | 5.46 |

Secondary: Percentage of rescue-free days during the last 3 weeks of the 6-week treatment period

| | |
|-----------------|---|
| End point title | Percentage of rescue-free days during the last 3 weeks of the 6-week treatment period |
|-----------------|---|

End point description:

Albuterol was provided as a rescue medication, and participants were required to record rescue medication use in the morning and in the evening. Participants recorded the number of inhalations of rescue medication in a daily eDiary. The number of days when rescue medication was not used ("rescue-free days") during the last 3 weeks of the 6-week treatment period were counted, and

percentage calculated by dividing by 21 and multiplying by 100. Analysis was done using mixed effect ANCOVA model for treatment effects, incorporating fixed effects of baseline, period, age, center, smoking status, and random effects of participant.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 4 to Week 6 | |

| End point values | FP + Placebo | FP + GSK2190915 100 mg | FP + GSK2190915 300 mg | FP + Montelukast |
|-------------------------------------|----------------------|------------------------|------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 92 ^[39] | 92 ^[40] | 92 ^[41] | 93 ^[42] |
| Units: Percentage of days | | | | |
| least squares mean (standard error) | 40.44 (± 3.05) | 42.43 (± 3.03) | 42.59 (± 3.04) | 42.77 (± 3.02) |

Notes:

[39] - ITT Population

[40] - ITT Population

[41] - ITT Population

[42] - ITT Population

| End point values | FP / Salmeterol | | | |
|-------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 95 ^[43] | | | |
| Units: Percentage of days | | | | |
| least squares mean (standard error) | 41.96 (± 3.03) | | | |

Notes:

[43] - ITT Population

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---------------------------------------|
| Comparison groups | FP + Placebo v FP + GSK2190915 100 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.367 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.992 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.35 |
| upper limit | 6.33 |

| Statistical analysis title | Statistical analysis 2 |
|----------------------------|---------------------------------------|
| Comparison groups | FP + Placebo v FP + GSK2190915 300 mg |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.332 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.147 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.2 |
| upper limit | 6.49 |

| | |
|---|---------------------------------|
| Statistical analysis title | Statistical analysis 3 |
| Comparison groups | FP + Placebo v FP + Montelukast |
| Number of subjects included in analysis | 185 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.277 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.331 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.88 |
| upper limit | 6.55 |

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 4 |
| Comparison groups | FP + Placebo v FP / Salmeterol |
| Number of subjects included in analysis | 187 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.467 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.521 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.59 |
| upper limit | 5.63 |

Secondary: Percentage of rescue-free nights during the last 3 weeks of the 6-week

treatment period

| | |
|-----------------|---|
| End point title | Percentage of rescue-free nights during the last 3 weeks of the 6-week treatment period |
|-----------------|---|

End point description:

Albuterol was provided as a rescue medication, and participants were required to record rescue medication use in the morning and in the evening. Participants recorded the number of inhalations of rescue medication in a daily eDiary. The number of nights when rescue medication was not used ("rescue-free nights") during the last 3 weeks of the 6-week treatment period were counted, and percentage calculated by dividing by 21 and multiplying by 100. Analysis was done using mixed effect ANCOVA model for treatment effects, incorporating fixed effects of baseline, period, age, center, smoking status, and random effects of participant.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 4 to Week 6

| End point values | FP + Placebo | FP + GSK2190915 100 mg | FP + GSK2190915 300 mg | FP + Montelukast |
|-------------------------------------|----------------------|------------------------|------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 92 ^[44] | 92 ^[45] | 92 ^[46] | 93 ^[47] |
| Units: Percentage of nights | | | | |
| least squares mean (standard error) | 45.12 (± 2.87) | 45.69 (± 2.85) | 48.79 (± 2.86) | 45.32 (± 2.85) |

Notes:

[44] - ITT Population

[45] - ITT Population

[46] - ITT Population

[47] - ITT Population

| End point values | FP / Salmeterol | | | |
|-------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 95 ^[48] | | | |
| Units: Percentage of nights | | | | |
| least squares mean (standard error) | 43.98 (± 2.85) | | | |

Notes:

[48] - ITT Population

Statistical analyses

| | |
|---|---------------------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | FP + Placebo v FP + GSK2190915 100 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.789 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.575 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.65 |
| upper limit | 4.8 |

| | |
|---|---------------------------------------|
| Statistical analysis title | Statistical analysis 2 |
| Comparison groups | FP + Placebo v FP + GSK2190915 300 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.087 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 3.669 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.54 |
| upper limit | 7.87 |

| | |
|---|---------------------------------|
| Statistical analysis title | Statistical analysis 3 |
| Comparison groups | FP + Placebo v FP + Montelukast |
| Number of subjects included in analysis | 185 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.923 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.84 |
| upper limit | 4.24 |

| | |
|-----------------------------------|--------------------------------|
| Statistical analysis title | Statistical analysis 4 |
| Comparison groups | FP + Placebo v FP / Salmeterol |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 187 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.571 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.137 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.08 |
| upper limit | 2.81 |

Secondary: Percentage of nights without awakenings due to asthma during the last 3 weeks of the 6-week treatment period

| | |
|-----------------|--|
| End point title | Percentage of nights without awakenings due to asthma during the last 3 weeks of the 6-week treatment period |
|-----------------|--|

End point description:

Night time asthma symptoms were recorded every morning upon rising, before taking any rescue or study medication and before assessing the PEF. Symptoms were recorded on a 5-point scale: 0 = no symptoms during the night, 1 = symptoms causing to wake once, 2 = symptoms causing to wake twice or more, 3 = symptoms causing to be awake most of the night, 4 = could not sleep due to severe symptoms. Participants recorded the symptoms in a daily eDiary. The number of nights with no awakenings due to asthma during the last 3 weeks of the 6-week treatment period were counted, and percentage calculated by dividing by 21 and multiplying by 100. Analysis was done using mixed effect ANCOVA model for treatment effects, incorporating fixed effects of baseline, period, age, center, smoking status, and random effects of participant.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 4 to Week 6

| End point values | FP + Placebo | FP + GSK2190915 100 mg | FP + GSK2190915 300 mg | FP + Montelukast |
|-------------------------------------|----------------------|------------------------|------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 92 ^[49] | 92 ^[50] | 92 ^[51] | 93 ^[52] |
| Units: Percentage of nights | | | | |
| least squares mean (standard error) | 37.21 (± 2.87) | 38.22 (± 2.85) | 40.55 (± 2.85) | 37.7 (± 2.84) |

Notes:

[49] - ITT Population

[50] - ITT Population

[51] - ITT Population

[52] - ITT Population

| End point values | FP / Salmeterol | | | |
|-------------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 95 ^[53] | | | |
| Units: Percentage of nights | | | | |
| least squares mean (standard error) | 38.47 (± 2.85) | | | |

Notes:

[53] - ITT Population

Statistical analyses

| | |
|---|---------------------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | FP + Placebo v FP + GSK2190915 100 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.668 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.014 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.64 |
| upper limit | 5.67 |

| | |
|---|---------------------------------------|
| Statistical analysis title | Statistical analysis 2 |
| Comparison groups | FP + Placebo v FP + GSK2190915 300 mg |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.156 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 3.349 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.29 |
| upper limit | 7.98 |

| | |
|-----------------------------------|---------------------------------|
| Statistical analysis title | Statistical analysis 3 |
| Comparison groups | FP + Placebo v FP + Montelukast |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 185 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.822 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.496 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.83 |
| upper limit | 4.82 |

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 4 |
| Comparison groups | FP + Placebo v FP / Salmeterol |
| Number of subjects included in analysis | 187 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.555 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.94 |
| upper limit | 5.46 |

Secondary: Number of participants withdrawn due to lack of efficacy during the last 3 weeks of the 6-week treatment period

| | |
|--|---|
| End point title | Number of participants withdrawn due to lack of efficacy during the last 3 weeks of the 6-week treatment period |
| End point description: | |
| <p>Participants were withdrawn if they met any of the following three criteria for 'lack of efficacy': 1) Clinic FEV1 below the FEV1 'Stability Limit' value, 2) During any consecutive 7-day period, the participant experienced PEF fallen below the PEF 'Stability Limit' for more than 3 days, or if ≥ 12 inhalations per day of albuterol were used for more than 2 days, and 3) Asthma exacerbation. The number of withdrawals due to lack of efficacy were summarized for each treatment and Fisher's Exact test was used for comparison with placebo add-on. Withdrawals occurring during active washout periods are not included.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Week 4 to Week 6 | |

| End point values | FP + Placebo | FP + GSK2190915 100 mg | FP + GSK2190915 300 mg | FP + Montelukast |
|-------------------------------|----------------------|------------------------|------------------------|----------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 104 ^[54] | 103 ^[55] | 96 ^[56] | 99 ^[57] |
| Units: Number of participants | 9 | 5 | 3 | 7 |

Notes:

[54] - ITT Population

[55] - ITT Population

[56] - ITT Population

[57] - ITT Population

| End point values | FP / Salmeterol | | | |
|-------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 104 ^[58] | | | |
| Units: Number of participants | 5 | | | |

Notes:

[58] - ITT Population

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---------------------------------------|
| Comparison groups | FP + Placebo v FP + GSK2190915 100 mg |
| Number of subjects included in analysis | 207 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.408 |
| Method | Fisher exact |
| Confidence interval | |
| level | 95 % |

| Statistical analysis title | Statistical analysis 2 |
|---|---------------------------------------|
| Comparison groups | FP + Placebo v FP + GSK2190915 300 mg |
| Number of subjects included in analysis | 200 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.138 |
| Method | Fisher exact |
| Confidence interval | |
| level | 95 % |

| Statistical analysis title | Statistical analysis 3 |
|-----------------------------------|---------------------------------|
| Comparison groups | FP + Placebo v FP + Montelukast |

| | |
|---|---------------|
| Number of subjects included in analysis | 203 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.797 |
| Method | Fisher exact |
| Confidence interval | |
| level | 95 % |

| | |
|---|--------------------------------|
| Statistical analysis title | Statistical analysis 4 |
| Comparison groups | FP + Placebo v FP / Salmeterol |
| Number of subjects included in analysis | 208 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.408 |
| Method | Fisher exact |
| Confidence interval | |
| level | 95 % |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment adverse events (AE) and serious adverse events (SAE) were collected from the start of treatment until the follow-up contact (a maximum of 178 days).

Adverse event reporting additional description:

On-treatment AEs and SAEs are reported for the ITT Population.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 14.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | FP + Placebo |
|-----------------------|--------------|

Reporting group description:

Participants received FP 100 µg oral inhalation twice daily (BID) for 6 weeks (first 3 weeks considered as active washout), in one of the 4 treatment periods. Placebo administered every morning (AM) was added to the dosing regimen. Blinding was maintained by administration of a montelukast-matching placebo capsule every evening (PM). Albuterol aerosol was provided as a rescue inhalation.

| | |
|-----------------------|------------------------|
| Reporting group title | FP + GSK2190915 100 mg |
|-----------------------|------------------------|

Reporting group description:

Participants received FP 100 µg oral inhalation BID for 6 weeks (first 3 weeks considered as active washout), in one of the 4 treatment periods. GSK2190915 100 mg AM was added to the dosing regimen. Blinding was maintained by PM administration of a montelukast-matching placebo capsule. Albuterol aerosol was provided as a rescue inhalation.

| | |
|-----------------------|------------------------|
| Reporting group title | FP + GSK2190915 300 mg |
|-----------------------|------------------------|

Reporting group description:

Participants received FP 100 µg oral inhalation BID for 6 weeks (first 3 weeks considered as active washout), in one of the 4 treatment periods. GSK2190915 300 mg AM was added to the dosing regimen. Blinding was maintained by PM administration of a montelukast-matching placebo capsule. Albuterol aerosol was provided as a rescue inhalation.

| | |
|-----------------------|------------------|
| Reporting group title | FP + Montelukast |
|-----------------------|------------------|

Reporting group description:

Participants received FP 100 µg oral inhalation BID for 6 weeks (first 3 weeks considered as active washout), in one of the 4 treatment periods. Montelukast 10 mg capsule administered PM was added to the dosing regimen. Blinding was maintained by AM administration of GSK2190915-matching placebo tablets. Albuterol aerosol was provided as a rescue inhalation.

| | |
|-----------------------|-----------------|
| Reporting group title | FP / Salmeterol |
|-----------------------|-----------------|

Reporting group description:

Participants received a combination of FP 100 µg and salmeterol 50 µg oral inhalation BID for 6 weeks (first 3 weeks considered as active washout), in one of the 4 treatment periods. Montelukast 10 mg capsule administered PM was added to the dosing regimen. Blinding was maintained by AM administration of GSK2190915-matching placebo tablets and PM administration of a montelukast-matching placebo capsule. Albuterol aerosol was provided as a rescue inhalation.

| Serious adverse events | FP + Placebo | FP + GSK2190915 100 mg | FP + GSK2190915 300 mg |
|---|-----------------|---------------------------|---------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | 1 / 103 (0.97%) | 0 / 96 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| Gastrointestinal disorders | | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | 1 / 103 (0.97%) | 0 / 96 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|------------------|-----------------|--|
| Serious adverse events | FP + Montelukast | FP / Salmeterol | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 99 (0.00%) | 0 / 104 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Gastrointestinal disorders | | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 99 (0.00%) | 0 / 104 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 3 %

| | | | |
|---|-----------------|---------------------------|---------------------------|
| Non-serious adverse events | FP + Placebo | FP + GSK2190915 100 mg | FP + GSK2190915 300 mg |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 104 (7.69%) | 3 / 103 (2.91%) | 4 / 96 (4.17%) |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 6 / 104 (5.77%) | 1 / 103 (0.97%) | 1 / 96 (1.04%) |
| occurrences (all) | 6 | 1 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 2 / 104 (1.92%) | 2 / 103 (1.94%) | 3 / 96 (3.13%) |
| occurrences (all) | 2 | 2 | 3 |

| | | | |
|---|------------------|-----------------|--|
| Non-serious adverse events | FP + Montelukast | FP / Salmeterol | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1 / 99 (1.01%) | 1 / 104 (0.96%) | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasopharyngitis | | | |

| | | | |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 1 / 99 (1.01%) | 1 / 104 (0.96%) | |
| occurrences (all) | 1 | 1 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 99 (0.00%) | 0 / 104 (0.00%) | |
| occurrences (all) | 0 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 13 October 2010 | To change the Medical Monitor, To provide rationale for only including females in the study, To change Inclusion Criterion to allow only female subjects to be enrolled into the study, To amend Inclusion Criterion so that the restriction on the FEV1/FVC ratio >0.70 applied to current and former subjects only, To remove the reference to oral (for example, bambuterol) or inhaled (for example, salmeterol/formoterol) long acting beta2-agonists being stopped on the morning prior to Visit 1 as these were already prohibited 2 weeks prior to Visit 1, To remove the adjustment for gender in the analyses. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported