Clinical trial results:
Bilastine and Montelukast in patients with Seasonal Allergic Rhinoconjunctivitis and Asthma: Efficacy of Concomitant Administration - the SKY Study

Summary

EudraCT number	2015-004806-40
Trial protocol	SK CZ PL LV HR IT
Global end of trial date	23 November 2016

Results information

Result version number	v1 (current)
This version publication date	07 March 2018
First version publication date	07 March 2018

Trial information

Trial identification

Sponsor protocol code	MEIN/15/Bil-ARC/001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Menarini International Operations Luxembourg S.A
Sponsor organisation address	1, Avenue de la Gare, Luxembourg, Luxembourg, L-1611
Public contact	Paolo Fabrizzi, Menarini International Operations Luxembourg S.A., +39 055 5680459, pfabrizzi@menarini.it
Scientific contact	Paolo Fabrizzi, Menarini International Operations Luxembourg S.A., +39 055 5680459, pfabrizzi@menarini.it

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	14 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 November 2016
Global end of trial reached?	Yes
Global end of trial date	23 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that concomitant administration of montelukast and bilastine is superior to bilastine monotherapy in SARC symptoms, as assessed by Total Symptoms Scores (TSS) after 4 weeks of treatment

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local law requirements

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 2016
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	Poland: 295
Country: Number of subjects enrolled	Slovakia: 21
Country: Number of subjects enrolled	Croatia: 5
Country: Number of subjects enrolled	Czech Republic: 72
Country: Number of subjects enrolled	Latvia: 23
Country: Number of subjects enrolled	Italy: 4
Worldwide total number of subjects	420
EEA total number of subjects	420

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)	420
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment started on 13 April 2016 and termineted on 23 November 2016.
454 patients with SARC and mild to moderate asthma as comorbidity were screened.
420 patients were randomised of which 388 patients completed the study.

Pre-assignment

Screening details:

454 patients with SARC and mild to moderate asthma as comorbidity were screened.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Bilastine Monotherapy

Arm description:

Bilastine 20 mg tablets + placebo tablets

Arm type	Experimental
Investigational medicinal product name	bilastine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

20 mg/die

Arm title	Montelukast Monotherapy

Arm description:

Montelukast 10 mg tablets + placebo tablets

Arm type	Experimental
Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg/die

Arm title	Bilastine + Montelukast

Arm description:

bilastine 20 mg tablets + montelukast 10 mg tablets

Arm type	Experimental

Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
10 mg/day

Investigational medicinal product name	bilastine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
20 mg/die

Number of subjects in period 1	Bilastine Monotherapy	Montelukast Monotherapy	Bilastine + Montelukast
Started	140	137	143
Completed	132	123	133
Not completed	8	14	10
Physician decision	1	1	-
Consent withdrawn by subject	3	4	4
Pregnancy	-	-	1
Drug intollerance	-	1	-
Lost to follow-up	-	-	1
Protocol deviation	4	8	4

Baseline characteristics

Reporting groups	
Reporting group title	Bilastine Monotherapy
Reporting group description:	
Bilastine 20 mg tablets + placebo tablets	
Reporting group title	Montelukast Monotherapy
Reporting group description:	
Montelukast 10 mg tablets + placebo tablets	
Reporting group title	Bilastine + Montelukast
Reporting group description:	
bilastine 20 mg tablets + montelukast 10 mg tablets	

Reporting group values	Bilastine Monotherapy	Montelukast Monotherapy	Bilastine + Montelukast
Number of subjects	140	137	143
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	140	137	143
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	35.5	35.4	34.9
standard deviation	± 11.0	± 10.7	± 11.1
Gender categorical Units: Subjects			
Female	83	73	69
Male	57	64	74

Reporting group values	Total		
Number of subjects	420		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	420		

From 65-84 years	0		
85 years and over	0		

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	225		
Male	195		

End points

End points reporting groups

Reporting group title	Bilastine Monotherapy
Reporting group description: Bilastine 20 mg tablets + placebo tablets	
Reporting group title	Montelukast Monotherapy
Reporting group description: Montelukast 10 mg tablets + placebo tablets	
Reporting group title	Bilastine + Montelukast
Reporting group description: bilastine 20 mg tablets + montelukast 10 mg tablets	
Subject analysis set title	Montelukast Monotherapy
Subject analysis set type	Intention-to-treat
Subject analysis set description: IIT population who have taken Montelukast	
Subject analysis set title	Bilastine Monotherapy
Subject analysis set type	Intention-to-treat
Subject analysis set description: IIT population for Bilastine Monotherapy	
Subject analysis set title	Bilastine + Montelukast
Subject analysis set type	Intention-to-treat
Subject analysis set description: IIT population for Bilastine + Montelukast therapy	

Primary: Montelukast+Bilastine is superior to Bilastine Monotherapy in SARC symptoms

End point title	Montelukast+Bilastine is superior to Bilastine Monotherapy in SARC symptoms
End point description: The primary objective of the study was to demonstrate that concomitant administration of Montelukast and Bilastine is superior to Bilastine monotherapy in SARC symptoms, assessed by total Symptoms Scores after 4 weeks of treatment.	
End point type	Primary
End point timeframe: 4 weeks of treatment (from baseline to 4 weeks of treatment)	

End point values	Bilastine Monotherapy	Bilastine + Montelukast		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	140	143		
Units: TSS score				
number (confidence interval 95%)	-3.4462 (-4.0708 to -2.8217)	-3.2522 (-3.8718 to -2.6327)		

Statistical analyses

Statistical analysis title	Montelukast+Bilastine vs Bilastine in TSS -4 weeks

Statistical analysis description:

Considering the ITT patients, the primary efficacy endpoint (i.e. the TSS) was assessed by analysis of covariance (ANCOVA) with the TSS change from baseline to after 4 weeks of treatment (calculated as difference in average post-baseline TSS to baseline TSS) as the dependent variable, treatment as fixed effect, centre as random effect, and baseline TSS as covariate.

Comparison groups	Bilastine Monotherapy v Bilastine + Montelukast
Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5721
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.194
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8693
upper limit	0.4813
Variability estimate	Standard error of the mean
Dispersion value	0.3429

Secondary: Montelukast+Bilastine compared with Montelukast and Bilastine monotherapies in asthma control

End point title	Montelukast+Bilastine compared with Montelukast and Bilastine monotherapies in asthma control

End point description:

To evaluate the efficacy of concomitant montelukast and bilastine compared with montelukast and bilastine monotherapies in asthma control, as assessed by Asthma Quality of Life Questionnaire (AQLQ) after 4 weeks and at the end of treatment.

End point type	Secondary

End point timeframe:

After 4 weeks of treatments and in the end of study (from baseline)

End point values	Montelukast Monotherapy	Bilastine Monotherapy	Bilastine + Montelukast	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	136	140	143	
Units: AQLQ SCORE				
number (confidence interval 95%)	0.5849 (0.4344 to 0.7353)	0.6399 (0.4929 to 0.7870)	0.6250 (0.4788 to 0.7712)	

Statistical analyses

Statistical analysis title	Bila vs Bila+Monte in asthma with AQLQ at 4 week
Comparison groups	Montelukast Monotherapy v Bilastine Monotherapy v Bilastine + Montelukast
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0105 [1]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.1552
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.0379
upper limit	-0.2725
Variability estimate	Standard error of the mean
Dispersion value	0.4489

Notes:

[1] - The P-value reported above refers to Bil vs Bil+Monte.

P-Value=0.5443 for Monte vs Bil+Monte.

P-Value=0.0645 for Bil vs Monte

Secondary: Montelukast+Bilastine compared with Montelukast and Bilastine monotherapies in SARC symptoms (DNSS)

End point title	Montelukast+Bilastine compared with Montelukast and Bilastine monotherapies in SARC symptoms (DNSS)

End point description:

To evaluate the efficacy of concomitant montelukast and bilastine compared with montelukast and bilastine monotherapies in daytime symptoms of SARC, as assessed by Daytime Nasal Symptom Score (DNSS) after 4 weeks of treatment.

End point type	Secondary

End point timeframe:

After 4 weeks of treatment (from baseline).

End point values	Montelukast Monotherapy	Bilastine Monotherapy	Bilastine + Montelukast	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	136	140	143	
Units: DNSS score				
number (confidence interval 95%)	-1.8678 (-2.2468 to -1.4888)	-2.1106 (-2.4863 to -1.7349)	-1.9713 (-2.3442 to -1.5984)	

Statistical analyses

Statistical analysis title	Bila vs Bila+Monte in SARC with DNSS at 4 weeks
Comparison groups	Montelukast Monotherapy v Bilastine Monotherapy v Bilastine + Montelukast

Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4885 [2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1393
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5342
upper limit	0.2557
Variability estimate	Standard error of the mean
Dispersion value	0.2009

Notes:

[2] - The P-Value above refers to Bil vs Bil+Monte.

P-Value= 0.6092 for Monte vs Bil+Monte

P-Value=0.2332 for Bil vs Monte

Secondary: Montelukast+Bilastine compared with Montelukast and Bilastine monotherapies in SARC symptoms (DNNSS)

End point title	Montelukast+Bilastine compared with Montelukast and Bilastine monotherapies in SARC symptoms (DNNSS)

End point description:

To evaluate the efficacy of concomitant montelukast and bilastine compared with montelukast and bilastine monotherapies in daytime symptoms of SARC, as assessed by Daytime Non Nasal Symptom Score (DNNSS) after 4 weeks of treatment.

End point type	Secondary

End point timeframe:

After 4 weeks of treatment (from baseline).

End point values	Montelukast Monotherapy	Bilastine Monotherapy	Bilastine + Montelukast	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	136	140	143	
Units: DNNSS score				
number (confidence interval 95%)	-1.1574 (-1.4462 to -0.8687)	-1.3185 (-1.6051 to -1.0320)	-1.2824 (-1.5667 to -0.9980)	

Statistical analyses

Statistical analysis title	Bila vs Bila+Monte in SARC with DNNSS at 4 weeks
Comparison groups	Bilastine Monotherapy v Montelukast Monotherapy v Bilastine + Montelukast

Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81032 [3]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.03615
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3319
upper limit	0.2596
Variability estimate	Standard error of the mean
Dispersion value	0.1504

Notes:

[3] - The P-Value above refers to Bil vs Bil+Monte.

P-Value= 0.5443 for Monte vs Bil+Monte

P-Value=0.0645 for Bil vs Monte

Secondary: Usage of relief medication for SARC

End point title	Usage of relief medication for SARC
End point description:	
Number of days without any relief medication for SARC.	
End point type	Secondary
End point timeframe:	
From baseline to 4 weeks of treatment.	

End point values	Montelukast Monotherapy	Bilastine Monotherapy	Bilastine + Montelukast	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	136	140	143	
Units: Days				
number (confidence interval 95%)	15.4179 (13.7642 to 17.0715)	15.8416 (14.2047 to 17.4785)	15.0057 (13.3817 to 16.6296)	

Statistical analyses

Statistical analysis title	Relief medication for SARC
Comparison groups	Montelukast Monotherapy v Bilastine Monotherapy v Bilastine + Montelukast

Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3704 [4]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.8359
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9969
upper limit	2.6688
Variability estimate	Standard error of the mean
Dispersion value	0.9322

Notes:

[4] - The P-Value above refers to Bil vs Bil+Monte.

P-Value= 0.6610 for Monte vs Bil+Monte

P-Value=0.6538 for Bil vs Monte

Secondary: Use of relief mediction for Asthma

End point title	Use of relief mediction for Asthma

End point description:

Number of days without any relief medication for Asthma.

End point type	Secondary

End point timeframe:

From baseline to 4 weeks of treatment.

End point values	Montelukast Monotherapy	Bilastine Monotherapy	Bilastine + Montelukast	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	136	140	143	
Units: Days				
number (confidence interval 95%)	50.7146 (46.3271 to 55.1021)	52.4177 (48.0780 to 56.7574)	53.2548 (48.9515 to 57.5580)	

Statistical analyses

Statistical analysis title	Relierf medication for Asthma
Comparison groups	Montelukast Monotherapy v Bilastine Monotherapy v Bilastine + Montelukast

Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7452 [5]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.837
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.8968
upper limit	4.2228
Variability estimate	Standard error of the mean
Dispersion value	2.5735

Notes:

[5] - The P-Value above refers to Bil vs Bil+Monte.

P-Value= 0.3278 for Monte vs Bil+Monte

P-Value= 0.5138 for Bil vs Monte

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entiere treatment period (85 days, 12 weeks).

Adverse event reporting additional description:

The tolerability was excellent with overall low rates of TEAEs, patient reporting TEAEs and TEAEs recorded as related to study medication during an entire treatment period of 85 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Bilastine
Reporting group description: -	
Reporting group title	Montelukast
Reporting group description: -	
Reporting group title	Bilastine + Montelukast
Reporting group description: -	

Serious adverse events	Bilastine	Montelukast	Bilastine + Montelukast
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 140 (0.00%)	1 / 137 (0.73%)	0 / 143 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 140 (0.00%)	1 / 137 (0.73%)	0 / 143 (0.00%)
occurrences causally related to treatment / all	0 / 5	1 / 14	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Bilastine	Montelukast	Bilastine + Montelukast
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 140 (2.86%)	14 / 137 (10.22%)	8 / 143 (5.59%)
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 140 (0.00%)	0 / 137 (0.00%)	2 / 143 (1.40%)
occurrences (all)	5	14	14
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 140 (0.00%)	0 / 137 (0.00%)	1 / 143 (0.70%)
occurrences (all)	5	14	14
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 140 (0.00%)	1 / 137 (0.73%)	1 / 143 (0.70%)
occurrences (all)	5	14	14
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 140 (0.00%)	2 / 137 (1.46%)	0 / 143 (0.00%)
occurrences (all)	5	14	14
Headache			
subjects affected / exposed	0 / 140 (0.00%)	1 / 137 (0.73%)	1 / 143 (0.70%)
occurrences (all)	5	14	14
Hypoaesthesia			
subjects affected / exposed	0 / 140 (0.00%)	1 / 137 (0.73%)	0 / 143 (0.00%)
occurrences (all)	5	14	14
Sedation			
subjects affected / exposed	0 / 140 (0.00%)	0 / 137 (0.00%)	1 / 143 (0.70%)
occurrences (all)	5	14	14
Somnolence			
subjects affected / exposed	2 / 140 (1.43%)	2 / 137 (1.46%)	2 / 143 (1.40%)
occurrences (all)	5	14	14
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 140 (0.71%)	0 / 137 (0.00%)	0 / 143 (0.00%)
occurrences (all)	5	14	14
Oedema peripheral			
subjects affected / exposed	0 / 140 (0.00%)	1 / 137 (0.73%)	0 / 143 (0.00%)
occurrences (all)	5	14	14
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 140 (0.71%)	0 / 137 (0.00%)	0 / 143 (0.00%)
occurrences (all)	5	14	14

Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 140 (0.00%)	1 / 137 (0.73%)	0 / 143 (0.00%)
occurrences (all)	5	14	14
Gingival bleeding			
subjects affected / exposed	0 / 140 (0.00%)	1 / 137 (0.73%)	0 / 143 (0.00%)
occurrences (all)	5	14	14
Hypoaesthesia oral			
subjects affected / exposed	0 / 140 (0.00%)	1 / 137 (0.73%)	0 / 143 (0.00%)
occurrences (all)	5	14	14
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 140 (0.00%)	1 / 137 (0.73%)	0 / 143 (0.00%)
occurrences (all)	5	14	14
Insomnia			
subjects affected / exposed	0 / 140 (0.00%)	0 / 137 (0.00%)	1 / 143 (0.70%)
occurrences (all)	5	14	14
Irritability			
subjects affected / exposed	0 / 140 (0.00%)	1 / 137 (0.73%)	0 / 143 (0.00%)
occurrences (all)	5	14	14
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	1 / 140 (0.71%)	0 / 137 (0.00%)	1 / 143 (0.70%)
occurrences (all)	5	14	14

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