Clinical trial results:
A 2 year prospective multicentre randomised controlled trial comparing effectiveness in daily practice of different treatment strategies for early RA

Summary

EudraCT number	2008-007225-39
Trial protocol	BE
Global end of trial date	30 June 2015

Results information

Result version number	v1 (current)
This version publication date	27 December 2018
First version publication date	27 December 2018

Trial information

Trial identification

Sponsor protocol code	CareRA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01172639
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospitals Leuven
Sponsor organisation address	herestraat 49, Leuven, Belgium, 3000
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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	01 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2015
Global end of trial reached?	Yes
Global end of trial date	30 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To study in patients with severe RA, the efficacy and effectiveness of a classic COBRA scheme (with 15mg MTX) versus two modified COBRA schemes respectively “slim” (without SSZ and with half dose steroids) and “avant-garde” (leflunomide instead of SSZ and half dose steroids) in daily practice.

To study in patients with less severe RA, the daily practice efficacy and effectiveness of a tight step up regimen (with 15mg MTX) versus a modified COBRA slim scheme (without SSZ and with half dose steroids).

Protection of trial subjects:

pragmatic trial rooted in daily practice, patient were started on therapy based on the remission induction principle and were followed by the treat to target principle which means treatment adaptations were done whenever patients failed to comply with low disease activity as defined in the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 379
Worldwide total number of subjects	379
EEA total number of subjects	379

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)	318
From 65 to 84 years	61
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

400 participants were recruited between Januari 2009 and May 2013. There were patients included in 13 Flemish rheumatology centers (2 academic centers, 7 general hospitals and 4 private practices)

Pre-assignment

Screening details:

there were 400 patients screened of which 379 were randomised to a treatment arm, 21 patients were not randomised: 1 screen failure, 10 withdrawals by subject, 10 randomisation errors

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CoBRA Classic High Risk Group

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Ledertrexate
Investigational medicinal product code	PA1327/009/001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

total dose of maximum 20 mg weekly (range from 7.5 to 20 mg weekly)

Investigational medicinal product name	Salazopyrine
Investigational medicinal product code	PA187/51/3
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

total dose of maximum 3gr (range from 1 to 3 gr daily) for a period of 40 weeks

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

Dosage and administration details:

weekly step down scheme starting with 60-40-25-20-15-10 mg daily for 6 weeks, followed by 7.5mg daily till week 28 of treatment then tapered down to stop at week 32

Arm title	CoBRA Slim High Risk Group

Arm description: -

Arm type	Active comparator

Investigational medicinal product name	Ledertrexate
Investigational medicinal product code	PA1327/009/001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

total dose of maximum 20 mg weekly (range from 7.5 to 20 mg weekly)

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

Dosage and administration details:

weekly step down scheme starting with 30-20-12.5-10-7.5 mg daily for 5 weeks, followed by 5mg daily till week 28 of treatment then tapered down to stop at week 32

Arm title	CoBRA Avant-Garde High Risk group

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Ledertrexate
Investigational medicinal product code	PA1327/009/001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

total dose of maximum 20 mg weekly (range from 7.5 to 20 mg weekly)

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

Dosage and administration details:

weekly step down scheme starting with 30-20-12.5-10-7.5 mg daily for 5 weeks, followed by 5mg daily till week 28 of treatment then tapered down to stop at week 32

Investigational medicinal product name	Leflunomide
Investigational medicinal product code	EU/1/99/118/001-004
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

range 10-20 mg daily, oral intake

Arm title	CoBRA Slim Low Risk Group

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Ledertrexate
Investigational medicinal product code	PA1327/009/001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

total dose of maximum 20 mg weekly (range from 7.5 to 20 mg weekly)

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

Dosage and administration details:

weekly step down scheme starting with 30-20-12.5-10-7.5 mg daily for 5 weeks, followed by 5mg daily till week 28 of treatment then tapered down to stop at week 32

Arm title	Tight Step Up Low Risk Group

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Ledertrexate
Investigational medicinal product code	PA1327/009/001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

total dose of maximum 20 mg weekly (range from 7.5 to 20 mg weekly)

Number of subjects in period 1	CoBRA Classic High Risk Group	CoBRA Slim High Risk Group	CoBRA Avant-Garde High Risk group
Started	98	98	93
Week 16	94	96	91
week 52	89	89	88
Completed	85	87	77
Not completed	13	11	16
Adverse event, serious fatal	1	1	-
Consent withdrawn by subject	3	3	5
Lost to follow-up	9	7	11

Number of subjects in period 1	CoBRA Slim Low Risk Group	Tight Step Up Low Risk Group
Started	43	47
Week 16	39	47
week 52	38	45
Completed	32	41
Not completed	11	6
Adverse event, serious fatal	-	-
Consent withdrawn by subject	5	-
Lost to follow-up	6	6

Baseline characteristics

Reporting groups	
Reporting group title	CoBRA Classic High Risk Group
Reporting group description: -	
Reporting group title	CoBRA Slim High Risk Group
Reporting group description: -	
Reporting group title	CoBRA Avant-Garde High Risk group
Reporting group description: -	
Reporting group title	CoBRA Slim Low Risk Group
Reporting group description: -	
Reporting group title	Tight Step Up Low Risk Group
Reporting group description: -	

Reporting group values	CoBRA Classic High Risk Group	CoBRA Slim High Risk Group	CoBRA Avant-Garde High Risk group
Number of subjects	98	98	93
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)	83	82	80
From 65-84 years	15	16	13
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	53.2	51.8	51.1
standard deviation	± 11.9	± 13.1	± 13.1
Gender categorical Units: Subjects			
Female	64	63	64
Male	34	35	29
RAce/Ethnicity Units: Subjects			
Caucasian	95	96	90
Hispanic	0	0	0
Asian	2	1	0
Black	1	1	1
North African	0	0	2
Smoking Status Units: Subjects			
Current	30	30	23
Past	26	28	33
Never	42	40	37

Symptom Duration			
Units: weeks			
arithmetic mean	33.8	33.2	44.3
standard deviation	± 35.5	± 38.2	± 65.9

Reporting group values	CoBRA Slim Low Risk Group	Tight Step Up Low Risk Group	Total
Number of subjects	43	47	379
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)	35	38	318
From 65-84 years	8	9	61
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	51.4	51.0	
standard deviation	± 14.4	± 14.0	-
Gender categorical			
Units: Subjects			
Female	33	38	262
Male	10	9	117
RAce/Ethnicity			
Units: Subjects			
Caucasian	43	47	371
Hispanic	0	0	0
Asian	0	0	3
Black	0	0	3
North African	0	0	2
Smoking Status			
Units: Subjects			
Current	10	4	97
Past	11	14	112
Never	22	29	170
Symptom Duration			
Units: weeks			
arithmetic mean	34.4	33.1	
standard deviation	± 68.2	± 62.2	-

End points

End points reporting groups

Reporting group title	CoBRA Classic High Risk Group
Reporting group description: -	
Reporting group title	CoBRA Slim High Risk Group
Reporting group description: -	
Reporting group title	CoBRA Avant-Garde High Risk group
Reporting group description: -	
Reporting group title	CoBRA Slim Low Risk Group
Reporting group description: -	
Reporting group title	Tight Step Up Low Risk Group
Reporting group description: -	

Primary: remission according to DAS28-CRP at week 16

End point title	remission according to DAS28-CRP at week 16

End point description:

Number of patients in remission according to DAS28-CRP (Disease Activity Score based on 28 joint count and C-reactive Protein) at week 16.

DAS28-CRP is calculated with the following formula : 0.56*SQRT TJC28+0.28*SQRTSJC28+0.36*ln (CRP+1)+0.014*GH+0.96 in which TJC is the tender joint count, SJC the Swollen Joint Count and GH the general health estimated by the patient on a Visual Analogue Scale (VAS).
A value below 2.6 is indicating remission, below or equal to 3.2 low disease activity, between 3.2 and 5.1 moderate disease activity and above 5.1 high disease activity.

End point type	Primary

End point timeframe:

week 16

End point values	CoBRA Classic High Risk Group	CoBRA Slim High Risk Group	CoBRA Avant-Garde High Risk group	CoBRA Slim Low Risk Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	98	98	93	43
Units: participants	69	72	61	25

End point values	Tight Step Up Low Risk Group			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: participants	23			

Statistical analyses

Statistical analysis title	proportion in remission at week 16

Statistical analysis description:

number of patients in remission defined by a disease activity score based on the 28 joint count and C reactive protein (DAS28-CRP) < 2.6

Comparison groups	CoBRA Classic High Risk Group v CoBRA Slim High Risk Group v CoBRA Avant-Garde High Risk group v CoBRA Slim Low Risk Group v Tight Step Up Low Risk Group
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	Chi-squared

Notes:

[1] - Population description, ITT (all randomised subjects included), missing data imputed with Expectation Maximization on complete w104 database.

Primary: remission according to DAS28-CRP at week 52

End point title	remission according to DAS28-CRP at week 52

End point description:

Number of patients in remission according to DAS28-CRP (Disease Activity Score based on 28 joint count and C-reactive Protein) at week 52.

DAS28-CRP is calculated with the following formula : 0.56*SQRT TJC28+0.28*SQRTSJC28+0.36*ln (CRP+1)+0.014*GH+0.96 in which TJC is the tender joint count, SJC the Swollen Joint Count and GH the general health estimated by the patient on a Visual Analogue Scale (VAS).
A value below 2.6 is indicating remission, below or equal to 3.2 low disease activity, between 3.2 and 5.1 moderate disease activity and above 5.1 high disease activity.

End point type	Primary

End point timeframe:

week 52

End point values	CoBRA Classic High Risk Group	CoBRA Slim High Risk Group	CoBRA Avant-Garde High Risk group	CoBRA Slim Low Risk Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	98	98	93	43
Units: participants	63	57	57	29

End point values	Tight Step Up Low Risk Group			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: participants	29			

Statistical analyses

Statistical analysis title	proportion of patients in remission at week 52

Statistical analysis description:

number of patients in remission defined by a disease activity score based on the 28 joint count and C reactive protein (DAS28-CRP) < 2.6

Comparison groups	CoBRA Classic High Risk Group v CoBRA Slim High Risk Group v CoBRA Avant-Garde High Risk group v CoBRA Slim Low Risk Group v Tight Step Up Low Risk Group
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.05
Method	Chi-squared

Notes:

[2] - Population description, ITT (all randomised subjects included), missing data imputed with Expectation Maximization on complete w104 database.

Primary: remission according to DAS28-CRP at week 104

End point title	remission according to DAS28-CRP at week 104

End point description:

Number of patients in remission according to DAS28-CRP (Disease Activity Score based on 28 joint count and C-reactive Protein) at week 104.

DAS28-CRP is calculated with the following formula : 0.56*SQRT TJC28+0.28*SQRTSJC28+0.36*ln (CRP+1)+0.014*GH+0.96 in which TJC is the tender joint count, SJC the Swollen Joint Count and GH the general health estimated by the patient on a Visual Analogue Scale (VAS).
A value below 2.6 is indicating remission, below or equal to 3.2 low disease activity, between 3.2 and 5.1 moderate disease activity and above 5.1 high disease activity.

End point type	Primary

End point timeframe:

week 104

End point values	CoBRA Classic High Risk Group	CoBRA Slim High Risk Group	CoBRA Avant-Garde High Risk group	CoBRA Slim Low Risk Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	98	98	93	43
Units: participants	64	71	69	29

End point values	Tight Step Up Low Risk Group			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: participants	34			

Statistical analyses

Statistical analysis title	proportion of patients in remission at week 104

Statistical analysis description:

number of patients in remission defined by a disease activity score based on the 28 joint count and C reactive protein (DAS28-CRP) < 2.6

Comparison groups	CoBRA Classic High Risk Group v CoBRA Slim High Risk Group v CoBRA Avant-Garde High Risk group v CoBRA Slim Low Risk Group v Tight Step Up Low Risk Group
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.05
Method	Chi-squared

Notes:

[3] - Population description, ITT (all randomised subjects included), missing data imputed with Expectation Maximization on complete w104 database.

Secondary: remission according to SDAI at week 16

End point title	remission according to SDAI at week 16

End point description:

Number of patients in remission according to SDAI (Simplified Disease Activity Index) at week 16.

SDAI is calculated with the following formula : TJC28+SJC28+GH+GA ph in which TJC is the number of tender joints, SJC the number of Swollen Joint and GH the general health assessed by the patient on a Visual Analogue Scale (VAS) and GA ph the general assessment of the physician on a VAS.
A value below 3.3 is indicating remission, between 3.4 and 11.0 low disease activity, between 11.1 and 26.0 moderate disease activity and above 26.0 high disease activity.

End point type	Secondary

End point timeframe:

week 16

End point values	CoBRA Classic High Risk Group	CoBRA Slim High Risk Group	CoBRA Avant-Garde High Risk group	CoBRA Slim Low Risk Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	98	98	93	43
Units: participants	42	33	44	12

End point values	Tight Step Up Low Risk Group			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: participants	12			

Statistical analyses

Statistical analysis title	proportion in remission at week 16 (SDAI)

Statistical analysis description:

number of patients in remission defined by a simplified disease activity score (SDAI<=3.3)

Comparison groups	CoBRA Classic High Risk Group v CoBRA Slim High Risk Group v CoBRA Avant-Garde High Risk group v CoBRA Slim Low Risk Group v Tight Step Up Low Risk Group
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.05
Method	Chi-squared

Notes:

[4] - Population description, ITT (all randomised subjects included), missing data imputed with Expectation Maximization on complete w104 database.

Secondary: remission according to SDAI at week 52

End point title	remission according to SDAI at week 52

End point description:

Number of patients in remission according to SDAI (Simplified Disease Activity Index) at week 52.

SDAI is calculated with the following formula : TJC28+SJC28+GH+GA ph in which TJC is the number of tender joints, SJC the number of Swollen Joint and GH the general health assessed by the patient on a Visual Analogue Scale (VAS) and GA ph the general assessment of the physician on a VAS.
A value below 3.3 is indicating remission, between 3.4 and 11.0 low disease activity, between 11.1 and 26.0 moderate disease activity and above 26.0 high disease activity.

End point type	Secondary

End point timeframe:

week 52

End point values	CoBRA Classic High Risk Group	CoBRA Slim High Risk Group	CoBRA Avant-Garde High Risk group	CoBRA Slim Low Risk Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	98	98	93	43
Units: participants	36	27	39	20

End point values	Tight Step Up Low Risk Group			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: participants	15			

Statistical analyses

Statistical analysis title	proportion in remission at week 52 (SDAI)

Statistical analysis description:	
number of patients in remission defined by a simplified disease activity score (SDAI<=3.3)	
Comparison groups	CoBRA Classic High Risk Group v CoBRA Slim High Risk Group v CoBRA Avant-Garde High Risk group v CoBRA Slim Low Risk Group v Tight Step Up Low Risk Group
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.05
Method	Chi-squared

Notes:

[5] - Population description, ITT (all randomised subjects included), missing data imputed with Expectation Maximization on complete w104 database.

Secondary: remission according to SDAI at week 104

End point title	remission according to SDAI at week 104

End point description:

Number of patients in remission according to SDAI (Simplified Disease Activity Index) at week 104.

SDAI is calculated with the following formula : TJC28+SJC28+GH+GA ph in which TJC is the number of tender joints, SJC the number of Swollen Joint and GH the general health assessed by the patient on a Visual Analogue Scale (VAS) and GA ph the general assessment of the physician on a VAS.
A value below 3.3 is indicating remission, between 3.4 and 11.0 low disease activity, between 11.1 and 26.0 moderate disease activity and above 26.0 high disease activity.

End point type	Secondary

End point timeframe:

week 104

End point values	CoBRA Classic High Risk Group	CoBRA Slim High Risk Group	CoBRA Avant-Garde High Risk group	CoBRA Slim Low Risk Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	98	98	93	43
Units: participants	31	28	41	20

End point values	Tight Step Up Low Risk Group			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: participants	13			

Statistical analyses

Statistical analysis title	proportion in remission at week 104(SDAI)

Statistical analysis description:

number of patients in remission defined by a simplified disease activity score (SDAI<=3.3)

Comparison groups	CoBRA Classic High Risk Group v CoBRA Slim High Risk Group v CoBRA Avant-Garde High Risk group v CoBRA Slim Low Risk Group v Tight Step Up Low Risk Group
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.05
Method	Chi-squared

Notes:

[6] - Population description, ITT (all randomised subjects included), missing data imputed with Expectation Maximization on complete w104 database.

Secondary: Clinically significant change in health assessment questionnaire (HAQ) score

End point title	Clinically significant change in health assessment questionnaire (HAQ) score

End point description:

Number of patients with a change of > 0.22 in the Health Assessment Questionnaire (HAQ) score over the period between baseline and week 104.

A change of > 0.22 in this score is considered as clinical relevant for reumatoid arthritis patients.

End point type	Secondary

End point timeframe:

Baseline to week 104

End point values	CoBRA Classic High Risk Group	CoBRA Slim High Risk Group	CoBRA Avant-Garde High Risk group	CoBRA Slim Low Risk Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	98	98	93	43
Units: participants	71	62	64	25

End point values	Tight Step Up Low Risk Group			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: participants	26			

Statistical analyses

Statistical analysis title	proportion of clinically significant change in HAQ

Statistical analysis description:

Number of patients with a change of >w 0.22 in the HAQ.

Comparison groups	CoBRA Classic High Risk Group v CoBRA Slim High Risk Group

	v CoBRA Avant-Garde High Risk group v CoBRA Slim Low Risk Group v Tight Step Up Low Risk Group
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.05
Method	Chi-squared

Notes:

[7] - Population description, ITT (all randomised subjects included), missing data imputed with Expectation Maximization on complete w104 database.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected over a two year period per patient	
Adverse event reporting additional description:	
All Adverse Events were registered by health care professionals questioning the patients at each visit.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	CoBRA Classic High Risk Group
Reporting group description: -	
Reporting group title	CoBRA Slim High Risk Group
Reporting group description: -	
Reporting group title	CoBRA Avant-Garde High Risk group
Reporting group description: -	
Reporting group title	CoBRA Slim Low Risk Group
Reporting group description: -	
Reporting group title	Tight Step Up Low Risk Group
Reporting group description: -	

Serious adverse events	CoBRA Classic High Risk Group	CoBRA Slim High Risk Group	CoBRA Avant-Garde High Risk group
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 98 (21.43%)	22 / 98 (22.45%)	16 / 93 (17.20%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Baker's cyst excision			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	3 / 98 (3.06%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cervix carcinoma			

subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 93 (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
Cholesteatoma			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung carcinoma cell type unspecified recurrent			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung operation	Additional description: diagnostic resection of lung nodulus, benign nodule on pathology		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotid gland enlargement	Additional description: neoplasm		
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nodule	Additional description: nodule submandibular salivary gland		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 93 (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
Vascular disorders			

Atrial septal defect			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 93 (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
Peripheral vascular disorder			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 93 (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
Coronary artery disease			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 93 (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
Surgical and medical procedures			
Abdominal operation			
subjects affected / exposed	1 / 98 (1.02%)	2 / 98 (2.04%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amygdalotomy			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hysterectomy			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liposuction	Additional description: upper limbs		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 93 (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
Orthopaedic procedure			

subjects affected / exposed	2 / 98 (2.04%)	1 / 98 (1.02%)	4 / 93 (4.30%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Anaphylactoid reaction	Additional description: after wasp sting		
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 93 (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
Interstitial lung disease			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis	Additional description: peribronchitis		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 93 (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
Product issues			
Mucositis management			

subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Post procedural complication			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic delivery			
subjects affected / exposed	1 / 98 (1.02%)	2 / 98 (2.04%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 98 (0.00%)	3 / 98 (3.06%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block	Additional description: third degree		
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Pain	Additional description: diffuse pain		
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Anaemia			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow disorder			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal polyp			

subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 93 (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
Volvulus			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	2 / 93 (2.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Hernia diaphragmatic repair			

subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	3 / 93 (3.23%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatic nerve neuropathy			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernia	Additional description: Lumbago		
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis	Additional description: flare of reumatoid arthritis		
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	2 / 93 (2.15%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis	Additional description: septic bursitis olecrani		
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	0 / 93 (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
Viral infection			
subjects affected / exposed	0 / 98 (0.00%)	0 / 98 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	CoBRA Slim Low	Tight Step Up Low	

	Risk Group	Risk Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 43 (20.93%)	7 / 47 (14.89%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Baker's cyst excision			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholesteatoma			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 43 (2.33%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung carcinoma cell type unspecified recurrent			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 43 (2.33%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung operation	Additional description: diagnostic resection of lung nodulus, benign nodule on pathology		
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotid gland enlargement	Additional description: neoplasm		
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodule	Additional description: nodule submandibular salivary gland		
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Atrial septal defect			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	0 / 43 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 43 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abdominal operation			
subjects affected / exposed	0 / 43 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Amygdalotomy			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hysterectomy			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liposuction	Additional description: upper limbs		
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthopaedic procedure			
subjects affected / exposed	0 / 43 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Anaphylactoid reaction	Additional description: after wasp sting		
subjects affected / exposed	0 / 43 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 43 (2.33%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis	Additional description: peribronchitis		
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Mucositis management			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post procedural complication			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic delivery			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 43 (2.33%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block	Additional description: third degree		
subjects affected / exposed	0 / 43 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Pain	Additional description: diffuse pain		
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 43 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow disorder			

subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 43 (4.65%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal polyp			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cystitis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Hernia diaphragmatic repair			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorder			
subjects affected / exposed	1 / 43 (2.33%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatic nerve neuropathy			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia	Additional description: Lumbago		
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis	Additional description: flare of reumatoid arthritis		
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial infection			

subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis	Additional description: septic bursitis olecrani		
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 43 (0.00%)	0 / 47 (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: 5 %

Non-serious adverse events	CoBRA Classic High Risk Group	CoBRA Slim High Risk Group	CoBRA Avant-Garde High Risk group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 98 (86.73%)	88 / 98 (89.80%)	84 / 93 (90.32%)
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 98 (9.18%)	8 / 98 (8.16%)	13 / 93 (13.98%)
occurrences (all)	9	8	13
Syncope			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	0 / 93 (0.00%)
occurrences (all)	1	0	0
Phlebitis	Additional description: venous insufficiency		
subjects affected / exposed	4 / 98 (4.08%)	5 / 98 (5.10%)	6 / 93 (6.45%)
occurrences (all)	5	5	6
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 98 (1.02%)	4 / 98 (4.08%)	0 / 93 (0.00%)
occurrences (all)	1	4	0
General disorders and administration site conditions			
Agitation			
subjects affected / exposed	6 / 98 (6.12%)	2 / 98 (2.04%)	10 / 93 (10.75%)
occurrences (all)	7	2	10

Dyspnoea			
subjects affected / exposed	4 / 98 (4.08%)	3 / 98 (3.06%)	5 / 93 (5.38%)
occurrences (all)	4	4	5
Fatigue			
subjects affected / exposed	7 / 98 (7.14%)	4 / 98 (4.08%)	4 / 93 (4.30%)
occurrences (all)	7	6	5
Flushing			
subjects affected / exposed	6 / 98 (6.12%)	4 / 98 (4.08%)	2 / 93 (2.15%)
occurrences (all)	6	4	2
Malaise	Additional description: general malaise		
subjects affected / exposed	9 / 98 (9.18%)	4 / 98 (4.08%)	5 / 93 (5.38%)
occurrences (all)	9	4	6
Hair disorder	Additional description: loss of hair		
subjects affected / exposed	7 / 98 (7.14%)	12 / 98 (12.24%)	19 / 93 (20.43%)
occurrences (all)	7	13	20
Hyperhidrosis			
subjects affected / exposed	7 / 98 (7.14%)	3 / 98 (3.06%)	6 / 93 (6.45%)
occurrences (all)	7	3	7
Insomnia			
subjects affected / exposed	8 / 98 (8.16%)	4 / 98 (4.08%)	2 / 93 (2.15%)
occurrences (all)	8	4	2
Sjogren's syndrome			
subjects affected / exposed	5 / 98 (5.10%)	2 / 98 (2.04%)	6 / 93 (6.45%)
occurrences (all)	5	2	6
Reproductive system and breast disorders			
Genital infection			
subjects affected / exposed	2 / 98 (2.04%)	2 / 98 (2.04%)	8 / 93 (8.60%)
occurrences (all)	2	2	9
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	9 / 98 (9.18%)	10 / 98 (10.20%)	20 / 93 (21.51%)
occurrences (all)	12	10	23
Cough			
subjects affected / exposed	9 / 98 (9.18%)	13 / 98 (13.27%)	7 / 93 (7.53%)
occurrences (all)	9	14	7
Dyspnoea			

subjects affected / exposed	4 / 98 (4.08%)	3 / 98 (3.06%)	5 / 93 (5.38%)
occurrences (all)	4	4	5
Upper respiratory tract infection			
subjects affected / exposed	28 / 98 (28.57%)	42 / 98 (42.86%)	29 / 93 (31.18%)
occurrences (all)	50	72	46
Injury, poisoning and procedural complications			
Traumatic delivery			
subjects affected / exposed	6 / 98 (6.12%)	1 / 98 (1.02%)	6 / 93 (6.45%)
occurrences (all)	7	1	7
Cardiac disorders			
Palpitations			
subjects affected / exposed	8 / 98 (8.16%)	3 / 98 (3.06%)	6 / 93 (6.45%)
occurrences (all)	9	3	6
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 98 (12.24%)	6 / 98 (6.12%)	9 / 93 (9.68%)
occurrences (all)	14	8	12
Skin discomfort	Additional description: paresthesia		
subjects affected / exposed	7 / 98 (7.14%)	8 / 98 (8.16%)	6 / 93 (6.45%)
occurrences (all)	9	8	7
Vertigo			
subjects affected / exposed	11 / 98 (11.22%)	7 / 98 (7.14%)	6 / 93 (6.45%)
occurrences (all)	11	8	7
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 98 (8.16%)	1 / 98 (1.02%)	5 / 93 (5.38%)
occurrences (all)	8	1	6
Eye disorders			
Eye infection			
subjects affected / exposed	6 / 98 (6.12%)	4 / 98 (4.08%)	5 / 93 (5.38%)
occurrences (all)	8	4	5
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	25 / 98 (25.51%)	23 / 98 (23.47%)	37 / 93 (39.78%)
occurrences (all)	27	26	46
Diarrhoea			

subjects affected / exposed	5 / 98 (5.10%)	11 / 98 (11.22%)	24 / 93 (25.81%)
occurrences (all)	5	12	28
Gastroenteritis			
subjects affected / exposed	8 / 98 (8.16%)	8 / 98 (8.16%)	8 / 93 (8.60%)
occurrences (all)	9	9	8
Nausea			
subjects affected / exposed	15 / 98 (15.31%)	21 / 98 (21.43%)	12 / 93 (12.90%)
occurrences (all)	16	25	14
Reflux gastritis			
subjects affected / exposed	5 / 98 (5.10%)	7 / 98 (7.14%)	2 / 93 (2.15%)
occurrences (all)	6	8	2
Hepatobiliary disorders			
Liver function test abnormal			
subjects affected / exposed	17 / 98 (17.35%)	15 / 98 (15.31%)	24 / 93 (25.81%)
occurrences (all)	22	19	25
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	2 / 98 (2.04%)	9 / 98 (9.18%)	12 / 93 (12.90%)
occurrences (all)	2	11	12
Pruritus			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	3 / 93 (3.23%)
occurrences (all)	0	1	3
Renal and urinary disorders			
Renal impairment	Additional description: renal insufficiency		
subjects affected / exposed	1 / 98 (1.02%)	2 / 98 (2.04%)	3 / 93 (3.23%)
occurrences (all)	1	2	4
Urinary tract infection			
subjects affected / exposed	6 / 98 (6.12%)	3 / 98 (3.06%)	7 / 93 (7.53%)
occurrences (all)	7	3	9
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 98 (15.31%)	7 / 98 (7.14%)	12 / 93 (12.90%)
occurrences (all)	15	8	13
Arthritis			
subjects affected / exposed	7 / 98 (7.14%)	4 / 98 (4.08%)	4 / 93 (4.30%)
occurrences (all)	8	4	4

Osteoarthritis			
subjects affected / exposed	2 / 98 (2.04%)	2 / 98 (2.04%)	6 / 93 (6.45%)
occurrences (all)	2	2	6
Back pain			
subjects affected / exposed	12 / 98 (12.24%)	19 / 98 (19.39%)	13 / 93 (13.98%)
occurrences (all)	13	22	14
Muscle contractions involuntary			
subjects affected / exposed	6 / 98 (6.12%)	5 / 98 (5.10%)	5 / 93 (5.38%)
occurrences (all)	7	6	5
Rotator cuff syndrome			
subjects affected / exposed	6 / 98 (6.12%)	0 / 98 (0.00%)	2 / 93 (2.15%)
occurrences (all)	6	0	2
Tendon disorder			
subjects affected / exposed	5 / 98 (5.10%)	9 / 98 (9.18%)	11 / 93 (11.83%)
occurrences (all)	5	9	12
Infections and infestations			
Aphthous ulcer			
subjects affected / exposed	2 / 98 (2.04%)	3 / 98 (3.06%)	8 / 93 (8.60%)
occurrences (all)	2	3	10
Influenza			
subjects affected / exposed	5 / 98 (5.10%)	10 / 98 (10.20%)	10 / 93 (10.75%)
occurrences (all)	6	10	10

Non-serious adverse events	CoBRA Slim Low Risk Group	Tight Step Up Low Risk Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 43 (79.07%)	45 / 47 (95.74%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 43 (9.30%)	1 / 47 (2.13%)	
occurrences (all)	4	1	
Syncope			
subjects affected / exposed	0 / 43 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Phlebitis	Additional description: venous insufficiency		
subjects affected / exposed	2 / 43 (4.65%)	1 / 47 (2.13%)	
occurrences (all)	2	1	
Surgical and medical procedures			

Tooth extraction			
subjects affected / exposed	3 / 43 (6.98%)	0 / 47 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Agitation			
subjects affected / exposed	3 / 43 (6.98%)	0 / 47 (0.00%)	
occurrences (all)	3	0	
Dyspnoea			
subjects affected / exposed	0 / 43 (0.00%)	4 / 47 (8.51%)	
occurrences (all)	0	4	
Fatigue			
subjects affected / exposed	2 / 43 (4.65%)	5 / 47 (10.64%)	
occurrences (all)	2	5	
Flushing			
subjects affected / exposed	2 / 43 (4.65%)	0 / 47 (0.00%)	
occurrences (all)	2	0	
Malaise	Additional description: general malaise		
subjects affected / exposed	2 / 43 (4.65%)	1 / 47 (2.13%)	
occurrences (all)	2	1	
Hair disorder	Additional description: loss of hair		
subjects affected / exposed	7 / 43 (16.28%)	6 / 47 (12.77%)	
occurrences (all)	7	6	
Hyperhidrosis			
subjects affected / exposed	3 / 43 (6.98%)	1 / 47 (2.13%)	
occurrences (all)	4	1	
Insomnia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Sjogren's syndrome			
subjects affected / exposed	2 / 43 (4.65%)	1 / 47 (2.13%)	
occurrences (all)	2	1	
Reproductive system and breast disorders			
Genital infection			
subjects affected / exposed	1 / 43 (2.33%)	0 / 47 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal			

disorders			
Bronchitis			
subjects affected / exposed	2 / 43 (4.65%)	3 / 47 (6.38%)	
occurrences (all)	2	3	
Cough			
subjects affected / exposed	1 / 43 (2.33%)	1 / 47 (2.13%)	
occurrences (all)	1	1	
Dyspnoea			
subjects affected / exposed	0 / 43 (0.00%)	4 / 47 (8.51%)	
occurrences (all)	0	4	
Upper respiratory tract infection			
subjects affected / exposed	14 / 43 (32.56%)	18 / 47 (38.30%)	
occurrences (all)	29	40	
Injury, poisoning and procedural complications			
Traumatic delivery			
subjects affected / exposed	0 / 43 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 43 (4.65%)	2 / 47 (4.26%)	
occurrences (all)	2	2	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 43 (4.65%)	3 / 47 (6.38%)	
occurrences (all)	2	3	
Skin discomfort	Additional description: paresthesia		
subjects affected / exposed	4 / 43 (9.30%)	0 / 47 (0.00%)	
occurrences (all)	5	0	
Vertigo			
subjects affected / exposed	4 / 43 (9.30%)	3 / 47 (6.38%)	
occurrences (all)	5	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 43 (4.65%)	2 / 47 (4.26%)	
occurrences (all)	2	3	
Eye disorders			

Eye infection			
subjects affected / exposed	1 / 43 (2.33%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 43 (25.58%)	9 / 47 (19.15%)	
occurrences (all)	14	9	
Diarrhoea			
subjects affected / exposed	1 / 43 (2.33%)	4 / 47 (8.51%)	
occurrences (all)	1	4	
Gastroenteritis			
subjects affected / exposed	8 / 43 (18.60%)	3 / 47 (6.38%)	
occurrences (all)	9	3	
Nausea			
subjects affected / exposed	10 / 43 (23.26%)	11 / 47 (23.40%)	
occurrences (all)	14	12	
Reflux gastritis			
subjects affected / exposed	1 / 43 (2.33%)	3 / 47 (6.38%)	
occurrences (all)	1	3	
Hepatobiliary disorders			
Liver function test abnormal			
subjects affected / exposed	6 / 43 (13.95%)	6 / 47 (12.77%)	
occurrences (all)	6	8	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	4 / 43 (9.30%)	5 / 47 (10.64%)	
occurrences (all)	5	5	
Pruritus			
subjects affected / exposed	3 / 43 (6.98%)	2 / 47 (4.26%)	
occurrences (all)	3	2	
Renal and urinary disorders			
Renal impairment	Additional description: renal insufficiency		
subjects affected / exposed	0 / 43 (0.00%)	4 / 47 (8.51%)	
occurrences (all)	0	6	
Urinary tract infection			
subjects affected / exposed	0 / 43 (0.00%)	3 / 47 (6.38%)	
occurrences (all)	0	3	

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 43 (11.63%)	3 / 47 (6.38%)	
occurrences (all)	5	4	
Arthritis			
subjects affected / exposed	2 / 43 (4.65%)	1 / 47 (2.13%)	
occurrences (all)	2	1	
Osteoarthritis			
subjects affected / exposed	3 / 43 (6.98%)	2 / 47 (4.26%)	
occurrences (all)	4	2	
Back pain			
subjects affected / exposed	3 / 43 (6.98%)	9 / 47 (19.15%)	
occurrences (all)	4	13	
Muscle contractions involuntary			
subjects affected / exposed	2 / 43 (4.65%)	4 / 47 (8.51%)	
occurrences (all)	2	4	
Rotator cuff syndrome			
subjects affected / exposed	1 / 43 (2.33%)	1 / 47 (2.13%)	
occurrences (all)	1	1	
Tendon disorder			
subjects affected / exposed	5 / 43 (11.63%)	2 / 47 (4.26%)	
occurrences (all)	5	3	
Infections and infestations			
Aphthous ulcer			
subjects affected / exposed	0 / 43 (0.00%)	5 / 47 (10.64%)	
occurrences (all)	0	5	
Influenza			
subjects affected / exposed	2 / 43 (4.65%)	4 / 47 (8.51%)	
occurrences (all)	3	5	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This pragmatic trial rooted in daily practice is an open label trial and no medication adherence is measured. The trial has a superiority design, so the non-superiority from CoBRA Classic and Avant-Garde vs Slim can be stated.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25359382

http://www.ncbi.nlm.nih.gov/pubmed/25889222

http://www.ncbi.nlm.nih.gov/pubmed/27432356