Clinical trial results:
A randomized, controlled, multi-center study on the effectiveness of Traumeel® S (both ointment and gel) in Terms of pain and function compared with a topical NSAID in athletes with acute ankle sprain.

Summary

EudraCT number	2008-007939-41
Trial protocol	ES
Global end of trial date	12 September 2011

Results information

Result version number	v1 (current)
This version publication date	14 September 2016
First version publication date	14 September 2016

Trial information

Trial identification

Sponsor protocol code	TRS-ESP 2008-007939-41

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01066520
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biologische Heilmittel Heel GmbH
Sponsor organisation address	Dr-Reckeweg-Strasse 2-4, Baden-Baden, Germany, 76532
Public contact	Dr. Gabriele Niemann, Biologische Heilmittel Heel GmbH, +49 7221 501-290, gabriele.niemann@heel.com
Scientific contact	Dr. Gabriele Niemann, Biologische Heilmittel Heel GmbH, +49 7221 501-290, gabriele.niemann@heel.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 March 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 September 2011
Global end of trial reached?	Yes
Global end of trial date	12 September 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Confirmatory proof of efficacy in terms of pain and function using a test for noninferiority (‘at least as good’) for Traumeel® S topical treatment as compared to diclofenac topical treatment for patients with ankle sprain.

Protection of trial subjects:

Standard protection of trial subjects according to ICH GCP requirements was applied.

Background therapy:

Rescue medication for pain control (paracetamol 500-mg tablets, up to four tablets daily) was recorded by the patients on the patient diary Cards.

Evidence for comparator:

Topical application of diclofenac significantly reduces pain and inflammation in acute and chronic conditions including ankle sprain. Moreover it is well tolerated, resulting mostly in mild, easily resolved local Skin irritation, and is associated with fewer side-effects than other topical NSAIDs.

Actual start date of recruitment	24 August 2009
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	Spain: 449
Worldwide total number of subjects	449
EEA total number of subjects	449

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)	3
Adults (18-64 years)	446

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

15 centers enrolled 299 subjects (stage I) starting 24 August 2009. 150 patients were randomized in 10 study centers in stage II (combined stages: 449 patients in 15 study centers). The study was conducted as a randomized, double-blinded, controlled two-stage study of athletes having an acute unilateral ankle sprain of the lateral ankle joint.

Pre-assignment

Screening details:

Subjects were selected among athletes who were in training (professional or as amateur) and had experienced an acute unilateral ankle sprain of the lateral ankle joint. Eligible patients were randomized to receive one of the following treatments of the ankle for 2 weeks:

- Traumeel® S ointment
- Traumeel® S gel
- Diclofenac gel

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	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Subjects were assigned in a 1:1:1 randomization (Traumeel® S ointment: Traumeel® S gel: Diclofenac) according to a randomization schedule generated by idv Datenanalyse und Versuchsplanung (Krailling, Germany). The study was partially double blind. The 3 IMPs were packed in identical containers. In the setting of a 3-arm randomization it was double-blind for Traumeel® S gel + diclofenac gel (subject and investigator) and single-blind for Traumeel® S ointment (investigator).

Arms

Are arms mutually exclusive?	Yes
Arm title	Analysed Safety Combined Stages Traumeel S Gel

Arm description:

150 Patients were randomized in both stages to this Group but 2 of them were not treated. Tthus, 148 were included to the analysed safety Group.

Arm type	Experimental
Investigational medicinal product name	Traumeel S Gel
Investigational medicinal product code	none
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

IMP was applied three times daily, 2 g of gel (strand of ca. 6 cm, as measured onto the provided dosing cards), to sufficiently cover
the area of the lesion, gently rubbing, wait 15 minutes before covering the treated Skin with clothing.
No shower or bath was allowed for at least one hour after applying the ointment or gel.
IMP was applied by the patient himself at each day of the study, in the morning, around noon and at late afternoon, until termination.

Investigational medicinal product name	Traumeel S Gel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

IMP was applied three times daily, 2 g of gel (strand of ca. 6 cm, as measured onto the provided dosing cards), to sufficiently cover the area of the lesion, gently rubbing, wait 15 minutes before covering the treated Skin with clothing. No shower or bath was allowed for at least one hour after applying the ointment or gel. IMP was applied by the patient himself at each day of the study, in the morning, around noon and at late afternoon, until termination.

Arm title	Safety Combined Stages Traumeel S ointment

Arm description:

All patients who have had at least one dose of medication and one contact with the investigator afterwards are analyzed for safety. 152 Patients were randomized in both stages to this Group and completed the Trial.

Arm type	Experimental
Investigational medicinal product name	Traumeel S ointment
Investigational medicinal product code	none
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

IMP was applied three times daily, 2 g of ointment (strand of ca. 6 cm, as measured onto the provided dosing cards), to sufficiently cover
the area of the lesion, gently rubbing, wait 15 minutes before covering the treated Skin with clothing. No shower or bath was allowed for at least one hour after applying the ointment or gel.
IMP was applied by the patient himself at each day of the study, in the morning, around noon and at late afternoon, until termination.

Arm title	Safety combined stages Diclofenac gel

Arm description:

All patients who have had at least one dose of medication and one contact with the investigator afterwards are analyzed for safety. 147 Patients were randomized in both stages to this Group and completed the Trial.

Arm type	Active comparator
Investigational medicinal product name	Diclofenac gel
Investigational medicinal product code	none
Other name	NSAID
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

2 g of gel three times daily, to sufficiently cover the area of the lesion, gently rubbing.

Number of subjects in period 1[1]	Analysed Safety Combined Stages Traumeel S Gel	Safety Combined Stages Traumeel S ointment	Safety combined stages Diclofenac gel
Started	148	152	147
Completed	148	152	147

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: 150 Patients were randomized in both stages to this group, however 2 patients were not treated. Thus, only 148
patients were analysed in the Traumeel S Gel safety Group.

Baseline characteristics

Reporting groups

Reporting group title	Analysed Safety Combined Stages Traumeel S Gel
Reporting group description:	
150 Patients were randomized in both stages to this Group but 2 of them were not treated. Tthus, 148 were included to the analysed safety Group.	
Reporting group title	Safety Combined Stages Traumeel S ointment
Reporting group description:	
All patients who have had at least one dose of medication and one contact with the investigator afterwards are analyzed for safety. 152 Patients were randomized in both stages to this Group and completed the Trial.	
Reporting group title	Safety combined stages Diclofenac gel
Reporting group description:	
All patients who have had at least one dose of medication and one contact with the investigator afterwards are analyzed for safety. 147 Patients were randomized in both stages to this Group and completed the Trial.	

Reporting group values	Analysed Safety Combined Stages Traumeel S Gel	Safety Combined Stages Traumeel S ointment	Safety combined stages Diclofenac gel
Number of subjects	148	152	147
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)	1	2	0
Adults (18-64 years)	147	150	147
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Data are available from the ITT Groups only			
Units: years			
arithmetic mean	27.9	28.3	27.2
standard deviation	± 6.68	± 6.63	± 6.5
Gender categorical			
Data are available on the ITT subgroup only.			
Units: Subjects			
Female	106	113	109
Male	42	39	38
Race			
Data are available from the ITT subgroup only.			
Units: Subjects			
Caucasian	141	147	142
Asian			
African	1	2	1
Latin American	6	3	4

Smoker			
Data are available on the ITT subgroup only.			
Units: Subjects			
YES	26	36	19
NO	122	116	128
Location			
Data are available on the ITT subgroup only.			
Units: Subjects			
LEFT	66	69	69
RIGHT	82	83	78
Location			
Data are available on the ITT subgroup only.			
Units: Subjects			
LEFT	66	69	69
RIGHT	82	83	78
BMI			
Units: kg/m2			
arithmetic mean			
standard deviation	±	±	±

Reporting group values	Total		
Number of subjects	447		
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)	3		
Adults (18-64 years)	444		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Data are available from the ITT Groups only			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Data are available on the ITT subgroup only.			
Units: Subjects			
Female	328		
Male	119		
Race			
Data are available from the ITT subgroup only.			
Units: Subjects			
Caucasian	430		
Asian	0		
African	4		
Latin American	13		

Smoker			
Data are available on the ITT subgroup only.			
Units: Subjects			
YES	81		
NO	366		
Location			
Data are available on the ITT subgroup only.			
Units: Subjects			
LEFT	204		
RIGHT	243		
Location			
Data are available on the ITT subgroup only.			
Units: Subjects			
LEFT	204		
RIGHT	243		
BMI			
Units: kg/m2			
arithmetic mean			
standard deviation	-		

Subject analysis sets

Subject analysis set title	ITT Combined Stages Traumeel Gel
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Group is a subgroup of the Safety combined stages Traumeel Gel Group and includes all patients who have had at least one dose of medication, at least one efficacy evaluation under medication, and are without severe protocol deviations (full Analysis set). The ITT analysis is defined as the first line efficacy analysis, being in the line of a pragmatic approach (i.e. the test Treatment should demonstrate its efficacy under conditions that are to be expected in everyday life).

Subject analysis set title	ITT combined stages Traumeel ointment
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Group is a subgroup of the Safety combined stages Traumeel Ointment Group and includes all patients who have had at least one dose of medication, at least one efficacy evaluation under medication, and are without severe protocol deviations (full Analysis set). The ITT analysis is defined as the first line efficacy analysis, being in the line of a pragmatic approach (i.e. the test Treatment should demonstrate its efficacy under conditions that are to be expected in everyday life).

Subject analysis set title	ITT combined stages Diclofenac Gel
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Group is a subgroup of the Safety combined stages Diclofenac Gel Group and includes all patients who have had at least one dose of medication, at least one efficacy evaluation under medication, and are without severe protocol deviations (full Analysis set). The ITT analysis is defined as the first line efficacy analysis, being in the line of a pragmatic approach (i.e. the test Treatment should demonstrate its efficacy under conditions that are to be expected in everyday life).

Reporting group values	ITT Combined Stages Traumeel Gel	ITT combined stages Traumeel ointment	ITT combined stages Diclofenac Gel
Number of subjects	140	143	137
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	143	137
From 65-84 years	0	0	0
85 years and over		0	0
Age continuous			
Data are available from the ITT Groups only			
Units: years			
arithmetic mean	27.7	28.3	27.1
standard deviation	± 6.62	± 6.58	± 6.05
Gender categorical			
Data are available on the ITT subgroup only.			
Units: Subjects			
Female	39	39	34
Male	101	104	103
Race			
Data are available from the ITT subgroup only.			
Units: Subjects			
Caucasian	133	138	132
Asian	0	0	0
African	1	2	1
Latin American	6	3	4
Smoker			
Data are available on the ITT subgroup only.			
Units: Subjects			
YES	22	35	18
NO	118	108	119
Location			
Data are available on the ITT subgroup only.			
Units: Subjects			
LEFT	28	35	42
RIGHT	112	108	95
Location			
Data are available on the ITT subgroup only.			
Units: Subjects			
LEFT	66	64	66
RIGHT	74	79	71
BMI			
Units: kg/m2			
arithmetic mean	23.6	24.1	23.5
standard deviation	± 2.9	± 3	± 2.8

End points

End points reporting groups

Reporting group title	Analysed Safety Combined Stages Traumeel S Gel

Reporting group description:

150 Patients were randomized in both stages to this Group but 2 of them were not treated. Tthus, 148 were included to the analysed safety Group.

Reporting group title	Safety Combined Stages Traumeel S ointment

Reporting group description:

All patients who have had at least one dose of medication and one contact with the investigator afterwards are analyzed for safety. 152 Patients were randomized in both stages to this Group and completed the Trial.

Reporting group title	Safety combined stages Diclofenac gel

Reporting group description:

All patients who have had at least one dose of medication and one contact with the investigator afterwards are analyzed for safety. 147 Patients were randomized in both stages to this Group and completed the Trial.

Subject analysis set title	ITT Combined Stages Traumeel Gel
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Group is a subgroup of the Safety combined stages Traumeel Gel Group and includes all patients who have had at least one dose of medication, at least one efficacy evaluation under medication, and are without severe protocol deviations (full Analysis set). The ITT analysis is defined as the first line efficacy analysis, being in the line of a pragmatic approach (i.e. the test Treatment should demonstrate its efficacy under conditions that are to be expected in everyday life).

Subject analysis set title	ITT combined stages Traumeel ointment
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Group is a subgroup of the Safety combined stages Traumeel Ointment Group and includes all patients who have had at least one dose of medication, at least one efficacy evaluation under medication, and are without severe protocol deviations (full Analysis set). The ITT analysis is defined as the first line efficacy analysis, being in the line of a pragmatic approach (i.e. the test Treatment should demonstrate its efficacy under conditions that are to be expected in everyday life).

Subject analysis set title	ITT combined stages Diclofenac Gel
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Group is a subgroup of the Safety combined stages Diclofenac Gel Group and includes all patients who have had at least one dose of medication, at least one efficacy evaluation under medication, and are without severe protocol deviations (full Analysis set). The ITT analysis is defined as the first line efficacy analysis, being in the line of a pragmatic approach (i.e. the test Treatment should demonstrate its efficacy under conditions that are to be expected in everyday life).

Primary: Percent Change from baseline VAS scale on Day 7

End point title	Percent Change from baseline VAS scale on Day 7

End point description:

End point type	Primary

End point timeframe:

The 100 mm VAS score was recorded at Baseline and on Days 4, 7, 14 and 42.

End point values	ITT Combined Stages Traumeel Gel	ITT combined stages Traumeel ointment	ITT combined stages Diclofenac Gel	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	140	142	136	
Units: mm				
arithmetic mean (standard deviation)	-65.63 (± 26.136)	-60.88 (± 29.633)	-64.54 (± 26.094)	

Statistical analyses

Statistical analysis title	Percent change in VAS scale Day 7
Comparison groups	ITT Combined Stages Traumeel Gel v ITT combined stages Traumeel ointment v ITT combined stages Diclofenac Gel
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.8205
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney effect size
Point estimate	0.5142
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	0.4
Variability estimate	Standard deviation

Notes:

[1] - The Mann-Whitney measure gives the probability that a randomly chosen patient from the test group is better off than a randomly chosen patient from the reference group. The lower inferiority margin is stipulated as 0.4, because this is halfway between a ‘relevant’ and a ‘small’ difference (0.36 and 0.44). If (at least as good) is proven for the lower equivalence bound 0.4 then the lower bound of the one-sided confidence interval could define post hoc even a tighter margin for than the value 0.4

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Informatiomn on adverse events was assessed during the complete study period of 14 days at each visit as follows: visit 2 (Day 4), visit 3 (Day 7) and visit 4 (Day 14).
and during follow up on visit 5, 6 weeks after visit 1 (Day0).

Adverse event reporting additional description:

Findings of physical examination and vital criteria were presented by descriptive statistics.
Adverse events (AEs) were categorized by primary system organ class (SOC) and MedDRA preferred terms coded using the MedDRA dictionary. The number, intensity, relation to study medication, and action taken was described by frequency tables.
Serious

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	Safety Combined Stages Traumeel S Gel

Reporting group description:

150 Patients were randomized in both stages to this group. 148 were included to the safety Group.

Reporting group title	Safety Combined Stages Traumeel S ointment

Reporting group description:

152 Patients were randomized in both stages to this Group and completed the Trial.

Reporting group title	Safety combined stages Diclofenac gel

Reporting group description:

147 Patients were randomized in both stages to this Group and completed the Trial.

Serious adverse events	Safety Combined Stages Traumeel S Gel	Safety Combined Stages Traumeel S ointment	Safety combined stages Diclofenac gel
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 148 (0.00%)	0 / 152 (0.00%)	0 / 147 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Safety Combined Stages Traumeel S Gel	Safety Combined Stages Traumeel S ointment	Safety combined stages Diclofenac gel
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 148 (9.46%)	11 / 152 (7.24%)	8 / 147 (5.44%)
Injury, poisoning and procedural complications			

Joint injury			
subjects affected / exposed	0 / 148 (0.00%)	1 / 152 (0.66%)	0 / 147 (0.00%)
occurrences (all)	0	1	0
Joint sprain			
subjects affected / exposed	1 / 148 (0.68%)	1 / 152 (0.66%)	1 / 147 (0.68%)
occurrences (all)	1	1	1
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 148 (3.38%)	3 / 152 (1.97%)	1 / 147 (0.68%)
occurrences (all)	5	7	1
Hypoaesthesia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 152 (0.66%)	0 / 147 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 148 (0.00%)	1 / 152 (0.66%)	0 / 147 (0.00%)
occurrences (all)	0	2	0
Swelling			
subjects affected / exposed	0 / 148 (0.00%)	0 / 152 (0.00%)	2 / 147 (1.36%)
occurrences (all)	0	0	3
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 148 (0.68%)	1 / 152 (0.66%)	1 / 147 (0.68%)
occurrences (all)	1	1	1
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 148 (0.68%)	0 / 152 (0.00%)	0 / 147 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	0 / 148 (0.00%)	3 / 152 (1.97%)	1 / 147 (0.68%)
occurrences (all)	0	4	1
Pruritus			
subjects affected / exposed	2 / 148 (1.35%)	2 / 152 (1.32%)	1 / 147 (0.68%)
occurrences (all)	2	2	1
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	2 / 148 (1.35%)	0 / 152 (0.00%)	0 / 147 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
influenza			
subjects affected / exposed	1 / 148 (0.68%)	0 / 152 (0.00%)	0 / 147 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 148 (1.35%)	0 / 152 (0.00%)	1 / 147 (0.68%)
occurrences (all)	2	0	1

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.

not applicable

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/11273971

http://www.ncbi.nlm.nih.gov/pubmed/14751943

http://www.ncbi.nlm.nih.gov/pubmed/9475896

http://www.ncbi.nlm.nih.gov/pubmed/11195774

http://www.ncbi.nlm.nih.gov/pubmed/17137000

http://www.ncbi.nlm.nih.gov/pubmed/23543522

http://www.ncbi.nlm.nih.gov/pubmed/11550833

http://www.ncbi.nlm.nih.gov/pubmed/23543517

http://www.ncbi.nlm.nih.gov/pubmed/15286056

http://www.ncbi.nlm.nih.gov/pubmed/15317652

http://www.ncbi.nlm.nih.gov/pubmed/15147585

http://www.ncbi.nlm.nih.gov/pubmed/15155436

http://www.ncbi.nlm.nih.gov/pubmed/11505416

http://www.ncbi.nlm.nih.gov/pubmed/3283007

http://www.ncbi.nlm.nih.gov/pubmed/10709306

http://www.ncbi.nlm.nih.gov/pubmed/15330450

http://www.ncbi.nlm.nih.gov/pubmed/16309613

http://www.ncbi.nlm.nih.gov/pubmed/21231861

http://www.ncbi.nlm.nih.gov/pubmed/19546098

http://www.ncbi.nlm.nih.gov/pubmed/21422934

http://www.ncbi.nlm.nih.gov/pubmed/11276181

http://www.ncbi.nlm.nih.gov/pubmed/20457737

http://www.ncbi.nlm.nih.gov/pubmed/14754753

http://www.ncbi.nlm.nih.gov/pubmed/18810189

http://www.ncbi.nlm.nih.gov/pubmed/10291102

http://www.ncbi.nlm.nih.gov/pubmed/16972714

http://www.ncbi.nlm.nih.gov/pubmed/16972715

http://www.ncbi.nlm.nih.gov/pubmed/16395993

http://www.ncbi.nlm.nih.gov/pubmed/7786985

http://www.ncbi.nlm.nih.gov/pubmed/15969304

http://www.ncbi.nlm.nih.gov/pubmed/1509217

http://www.ncbi.nlm.nih.gov/pubmed/2197679

http://www.ncbi.nlm.nih.gov/pubmed/16781589

http://www.ncbi.nlm.nih.gov/pubmed/18346625

http://www.ncbi.nlm.nih.gov/pubmed/18937623

http://www.ncbi.nlm.nih.gov/pubmed/18279583

http://www.ncbi.nlm.nih.gov/pubmed/19380203