Clinical trial results:
An Actual Use Trial In A Simulated OTC Environment of an Extended-Release Over-the-Counter NSAID

Summary

EudraCT number	2014-005316-41
Trial protocol	Outside EU/EEA
Global end of trial date	28 December 2011

Results information

Result version number	v1
This version publication date	12 July 2016
First version publication date	26 July 2015

Trial information

Trial identification

Sponsor protocol code	BAYH6689/15647

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01427803
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer HealthCare AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com
Scientific contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.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	28 December 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 December 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

An actual use trial was designed to demonstrate whether consumers will exceed the labeled daily dose of Aleve 24 Hour at an unacceptable rate. Two aspects of consumer use of Aleve 24 Hour were examined: 1) the frequency at which consumers exceed the label-defined daily dose, thus putting themselves at clinical risk, and 2) the reasons for exceeding the labeled daily dose.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects and/or their legally authorized representative. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 778
Worldwide total number of subjects	778
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	4

Adults (18-64 years)	651
From 65 to 84 years	119
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Thirty two sites in the United States enrolled subjects in the trial between 14 September 2011 (First subject first visit) and 28 December 2011 (Last subject last visit).

Pre-assignment

Screening details:

The total 1931 subjects were screened over the telephone, 924 subjects began the enrollment interview, 778 subjects were randomized, and 777 subjects purchased product.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Patterns of Use Cohort

Arm description:

A subject was included in the Patterns of Use User Population if he/she completed the enrollment interview, purchased the investigational product, was randomized into the Patterns of Use Cohort, and provided e-diary data regarding their use.

Arm type	Experimental
Investigational medicinal product name	Naproxen Sodium Extended Release (ER) Tablet
Investigational medicinal product code	BAYH6689
Other name	Aleve 24 Hour
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

660 milligram Naproxen Sodium extended release tablet orally administered.

Arm title	Reasons for Misuse Cohort

Arm description:

A subject was included in the Reasons for Misuse Interviewed Population if he/she completed the enrollment interview, purchased the investigational product, was randomized into the Reasons for Misuse Cohort, misused on one or more occasions (did not comply with the label directions [took more than one tablet per dose or a subsequent dose less than 22 hours later]), and completed the reasons for misuse questions.

Arm type	Experimental
Investigational medicinal product name	Naproxen Sodium Extended Release Tablet
Investigational medicinal product code	BAYH6689
Other name	Aleve 24 Hour
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

660 milligram Naproxen Sodium extended release tablet orally administered.

Number of subjects in period 1	Patterns of Use Cohort	Reasons for Misuse Cohort
Started	526	252
Purchased Product	525	252
Took Product	508	237
Baseline Assessment	516	130 [1]
Completed	463	226
Not completed	63	26
Physician decision	3	-
'Did not take product '	1	-
Withdrawal by Subject	20	-
Lost to follow-up	32	26
Unable to complete full treatment period	6	-
'Protocol violation '	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only interviewed subjects were assessed for the baseline assessment and hence, number of subjects for baseline assessment were less than number of subjects completed the study period.

Baseline characteristics

Reporting groups	
Reporting group title	Patterns of Use Cohort
Reporting group description:	
A subject was included in the Patterns of Use User Population if he/she completed the enrollment interview, purchased the investigational product, was randomized into the Patterns of Use Cohort, and provided e-diary data regarding their use.	
Reporting group title	Reasons for Misuse Cohort
Reporting group description:	
A subject was included in the Reasons for Misuse Interviewed Population if he/she completed the enrollment interview, purchased the investigational product, was randomized into the Reasons for Misuse Cohort, misused on one or more occasions (did not comply with the label directions [took more than one tablet per dose or a subsequent dose less than 22 hours later]), and completed the reasons for misuse questions.	

Reporting group values	Patterns of Use Cohort	Reasons for Misuse Cohort	Total
Number of subjects	526	252	778
Age categorical Units: subjects			
12 to 17 Years	3	0	3
18 to 24 Years	25	4	29
25 to 34 Years	63	13	76
35 to 44 Years	81	28	109
45 to 54 Years	142	30	172
55 Years or Older	202	55	257
Not recorded	10	122	132
Gender categorical Units: subjects			
Female	295	68	363
Male	221	62	283
Not recorded	10	122	132

End points

End points reporting groups

Reporting group title	Patterns of Use Cohort

Reporting group description:

A subject was included in the Patterns of Use User Population if he/she completed the enrollment interview, purchased the investigational product, was randomized into the Patterns of Use Cohort, and provided e-diary data regarding their use.

Reporting group title	Reasons for Misuse Cohort

Reporting group description:

A subject was included in the Reasons for Misuse Interviewed Population if he/she completed the enrollment interview, purchased the investigational product, was randomized into the Reasons for Misuse Cohort, misused on one or more occasions (did not comply with the label directions [took more than one tablet per dose or a subsequent dose less than 22 hours later]), and completed the reasons for misuse questions.

Subject analysis set title	Naproxen Sodium ER (BAYH6689)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects were allowed to purchase a maximum of two bottles of Naproxen Sodium ER during their participation in the trial. The package instructed subjects to take one tablet every 24 hours while symptoms lasted for no more than 10 consecutive days for pain and no more than three consecutive days for fever.

Primary: Estimated Percentage of Misuse for Non-Therapeutic Reasons

End point title	Estimated Percentage of Misuse for Non-Therapeutic Reasons[1]

End point description:

The primary objective of this trial was to determine the percentage of non-therapeutic misuse. Two aspects of consumer use of Aleve 24 Hour were examined: the frequency at which consumers exceeded the label-defined daily dose modified by those who did so for non-therapeutic reasons.
Subjects in Patterns of Use cohort who took the product and subjects in Reason for Misuse cohort who completed interview were included in this analysis.

End point type	Primary

End point timeframe:

28 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Naproxen Sodium ER (BAYH6689)			
Subject group type	Subject analysis set			
Number of subjects analysed	632			
Units: Percentage of subjects				
number (not applicable)	6.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Non-therapeutic Reasons for Misuse

End point title	Non-therapeutic Reasons for Misuse

End point description:

Those subjects in the Reasons for Misuse Cohort who did not state misuse due to need for additional pain relief were categorized to Non-therapeutic misuse. Subjects in Reason for Misuse cohort who misused the product due to non-therapeutic reasons were included in this analysis.

End point type	Secondary

End point timeframe:

28 days

End point values	Naproxen Sodium ER (BAYH6689)			
Subject group type	Subject analysis set			
Number of subjects analysed	130			
Units: subjects				
number (not applicable)	52			

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated Percentage of Misuse for Non-Therapeutic Reasons Using the First 10-Day Treatment Course

End point title	Estimated Percentage of Misuse for Non-Therapeutic Reasons Using the First 10-Day Treatment Course

End point description:

This endpoint was an assessment of whether the rate of non-therapeutic misuse exceeded the pre-defined acceptable threshold for non-therapeutic misuse. The difference lay in the estimation of misuse in the Patterns of Use Cohort by using 10-day treatment courses rather than by "use day". A treatment course for each subject began on the first day they recorded taking one or more tablets which was followed by nine consecutive "evaluable days."
Subjects in Patterns of Use cohort who took the product and Reasons for misuse interviewed population were included in this analysis.

End point type	Secondary

End point timeframe:

28 days

End point values	Naproxen Sodium ER (BAYH6689)			
Subject group type	Subject analysis set			
Number of subjects analysed	632			
Units: Percentage of subjects				
number (not applicable)	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Took >/= 2 Tablets/Use Day in Any 10 Use Days

End point title	Percentage of Subjects Took >/= 2 Tablets/Use Day in Any 10 Use Days

End point description:

Percentage of subjects took greater than or equal to (>/=) 2 tablets/use day in any 10 use days thus exceeding the label directions during a treatment course. Subjects in Patterns of Use User Population who had at least 10 use days of the product were included in this analysis.

End point type	Secondary

End point timeframe:

28 days

End point values	Naproxen Sodium ER (BAYH6689)			
Subject group type	Subject analysis set			
Number of subjects analysed	375			
Units: Percentage of subjects				
number (not applicable)	14.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Took Product With Mean Daily Use >/= 2 Tablets /Use Day

End point title	Percentage of Subjects Who Took Product With Mean Daily Use >/= 2 Tablets /Use Day

End point description:

Percentage of subjects who took product with mean daily use >/= 2 tablets /use day thus exceeding the label directions on any use day. Subjects in Patterns of Use User Population who had at least 10 use days of the product were included in this analysis.

End point type	Secondary

End point timeframe:

28 days

End point values	Naproxen Sodium ER (BAYH6689)			
Subject group type	Subject analysis set			
Number of subjects analysed	375			
Units: Percentage of subjects				
number (not applicable)	4.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With at Least One Dosing Occasion Where More Than One Tablet Was Taken

End point title	Percentage of Subjects With at Least One Dosing Occasion Where More Than One Tablet Was Taken

End point description:

Percentage of subjects with at least one dosing occasion where more than one tablet was taken thus exceeding the label directions. Subjects in Patterns of Use cohort who took the product were included in the analysis.

End point type	Secondary

End point timeframe:

28 days

End point values	Naproxen Sodium ER (BAYH6689)			
Subject group type	Subject analysis set			
Number of subjects analysed	502			
Units: Percentage of subjects				
number (not applicable)	19.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Dosing Occasions Where More Than One Tablet Was Taken

End point title	Percentage of Dosing Occasions Where More Than One Tablet Was Taken

End point description:

Percentage of dosing occasions where more than one tablet was taken thus exceeding the label directions. Subjects in Patterns of Use cohort who took the product were included in this analysis.

End point type	Secondary

End point timeframe:

28 days

End point values	Naproxen Sodium ER (BAYH6689)			
Subject group type	Subject analysis set			
Number of subjects analysed	502[2]			
Units: Percentage of dosing occasions				
number (not applicable)	5.4			

Notes:

[2] - Number of Dosing occasions Analyzed = 9895.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Where a Dose Was Taken Less Than 22 Hours After the Most Recent Previous Dose

End point title	Percentage of Subjects Where a Dose Was Taken Less Than 22 Hours After the Most Recent Previous Dose

End point description:

Percentage of subjects where a dose was taken less than 22 hours after the most recent previous dose thus exceeding the label directions. 22 hours was chosen to allow for some imprecision in subjects' recollection. Subjects in Patterns of Use cohort who took the product were included in this analysis.

End point type	Secondary

End point timeframe:

28 days

End point values	Naproxen Sodium ER (BAYH6689)			
Subject group type	Subject analysis set			
Number of subjects analysed	502			
Units: Percentage of subjects				
number (not applicable)	72.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Dosing Occasions Where a Dose Was Taken Less Than 22 Hours After the Most Recent Previous Dose

End point title	Percentage of Dosing Occasions Where a Dose Was Taken Less Than 22 Hours After the Most Recent Previous Dose

End point description:

Percentage of dosing occasions where a dose was taken less than 22 hours after the most recent previous dose. 22 hours was chosen to allow for some imprecision in subjects' recollection. Subjects in Patterns of Use cohort who took the product were included in this analysis.

End point type	Secondary

End point timeframe:

28 days

End point values	Naproxen Sodium ER (BAYH6689)			
Subject group type	Subject analysis set			
Number of subjects analysed	502[3]			
Units: Percentage of dosing occasions				
number (not applicable)	27.8			

Notes:

[3] - Number of Dosing occasions Analyzed = 9895.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

28 days

Adverse event reporting additional description:

Adverse events were collected at the Follow-up telephone interview after completion of the 28 day Use Phase or sooner if they discontinued from the study. The safety population consisted of all subjects who took product. Safety data from the two cohorts were pooled in one group as both cohorts received the same treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Naproxen Sodium ER (BAYH6689)

Reporting group description:

Subjects were allowed to purchase a maximum of two bottles of Naproxen Sodium ER during their participation in the trial. The package instructed subjects to take one tablet every 24 hours while symptoms lasted for no more than 10 consecutive days for pain and no more than three consecutive days for fever.

Serious adverse events	Naproxen Sodium ER (BAYH6689)		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 745 (0.81%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
overdose			
subjects affected / exposed	1 / 745 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
cardiac failure congestive			
subjects affected / exposed	1 / 745 (0.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
hypersensitivity			

subjects affected / exposed	1 / 745 (0.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
diarrhea haemorrhagic			
subjects affected / exposed	1 / 745 (0.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
gallbladder disorder			
subjects affected / exposed	1 / 745 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
viral infection			
subjects affected / exposed	1 / 745 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Naproxen Sodium ER (BAYH6689)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	89 / 745 (11.95%)		
Nervous system disorders			
headache			
subjects affected / exposed	14 / 745 (1.88%)		
occurrences (all)	15		
Gastrointestinal disorders			
constipation			
subjects affected / exposed	12 / 745 (1.61%)		
occurrences (all)	12		
abdominal pain upper			
subjects affected / exposed	14 / 745 (1.88%)		
occurrences (all)	15		
diarrhoea			

subjects affected / exposed occurrences (all)	11 / 745 (1.48%) 11		
Musculoskeletal and connective tissue disorders back pain subjects affected / exposed occurrences (all)	 8 / 745 (1.07%) 8		
Infections and infestations nasopharyngitis subjects affected / exposed occurrences (all) sinusitis subjects affected / exposed occurrences (all)	 20 / 745 (2.68%) 20 10 / 745 (1.34%) 10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 September 2011	The amendment included below changes - - Added upper age limit for assent for subjects in Alabama - Added Rapid Estimate of Adult Literacy in Medicine (REALM) Teen Test - Added condition for closing enrollment for non-heavy users - Added follow-up for unresolved Adverse events at completion or early discontinuation of study - Changed when subjects were sent a reminder via the e-diary from "only if thy missed entry for that day" to "regardless of entering data for that day" - Specified that adverse event severity and relationship to investigational product would be assigned by the principal investigator at PEGUS physician.
03 November 2011	This amendment included below changes - - Added telephone contact with subjects who had missing e-diary days after 28 days to ask about product use on days subject did not make e-diary entries, if applicable - Clarified that enrollment would be closed after approximately 500 subjects had been enrolled into the Patterns of Use Cohort. - Added end-of-study e-diary review and process for subject to review and add information to e-diary prior to returning it - Adjusted sample size from 400 to 500 based on estimated percentage of subjects who would provide detailed use information.

Notes:

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.

Decimal places were automatically truncated if last decimal equals zero.

Notes: