SYNOPSIS

Name of Sponsor/ Company: Gebro Pharma GmbH	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Seractil® 400 mg powder for oral suspension	**Volume:**	
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Name of Active Ingredient: Dexibuprofen		

Title of Study:
Prospective, clinical trial to investigate safety, tolerability and efficacy of Dexibuprofen Gebro 400 mg powder for oral suspension (test) compared to Ibuprofen 400 mg powder for oral suspension (reference) in patients suffering from osteoarthritis of the hip or knee

Investigators:

Trial centre 1: Prim. Dr. Reinhold Hawel

Trial centre 2: Prim. MedR. Dr. Helmut Schwann

Trial centre 3: OA Dr. Omid Zamani

Study Centre(s):

Trial centre 1:	Rehabilitationszentrum für Erkrankungen des rheumatischen Formenkreises Salzburger Straße 26-30 5630 Bad Hofgastein
Trial centre 2:	Sonderkrankenanstalt für rheumatische Erkrankungen und Herz-Kreislaufkrankheiten Thorerstraße 26, 5760 Saalfelden
Trial centre 3:	Rheuma Zentrum Favoriten Dr. Omid Zamani Quellenstraße 181 1100 Wien

Publication (reference): n.a.

Studied period (years): 28.10.2009 (date of first enrolment) 15.06.2012 (date of last completed)	**Phase of development:** Phase IV Study

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Objectives:

- To evaluate and compare the tolerability profile of Dexibuprofen Gebro 400 mg powder for oral suspension compared to Ibuprofen 400 mg powder for oral suspension in patients with painful osteoarthritis of the hip or knee
- To compare the overall efficacy of Dexibuprofen Gebro 400 mg powder for oral suspension compared to Ibuprofen 400 mg powder for oral suspension in patients suffering from different complaints due to painful osteoarthritis of the hip or knee

Methodology:

Observer blinded, multi centre, randomized, parallel group, active controlled, non-inferiority trial of phase IV

Number of patients (planned and analysed):

planned: 480 randomised subjects

analysed: 489 subjects, 3 screening failures, 3 subjects did not take the IMP

Diagnosis and main criteria for inclusion:

Diagnosis: Osteoarthritis of hip or knee

Inclusion criteria:
male or female patients; age between 18 and 85 years; informed consent of the patient; everyday joint pain for the past three months; global pain intensity in the involved joint (hip or knee) of at least “moderate” within the last 48 h
[VRS]: moderate: recognizable impairment of the quality of life, pain at single functional sequences, pain dimension is limited to any time of the day

Inclusion criteria – osteoarthritis of hip
Confirmed diagnosis of painful osteoarthritis of the hip (according to Lequesne 1980)

Clinical parameters:
Restrictions of movement and pain caused by at least three motions in the affected hip: bending, bending with simultaneous adduction, extension, external rotation, internal rotation, abduction, adduction

Radiographic parameters:
Joint space narrowing in the frontal pelvic view and/or oblique view (in standing position), osteophytosis and/or bone tissue compaction or cysts

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Inclusion criteria – osteoarthritis of knee
Confirmed diagnosis of painful osteoarthritis of the knee (according to Lequesne 1980)

Clinical parameters:
Restriction of movement and pain caused by bending and stretching motions in the affected knee

Radiographic parameters:
Narrowing of articulation in the femurotibial (frontal) or femuropatellar (axial) part - osteophytosis and/or bone tissue compaction and/or cysts

Test product, dose and mode of administration, batch number:
Dexibuprofen Gebro 400 mg powder for oral suspension, strength: 400 mg, single oral dose (Seractil®), b.i.d

Manufacturer: Gebro Pharma GmbH, Austria
Batch number: 198905, 524112
Daily dose: 800 mg

Reference therapy, dose and mode of administration, batch number:
Ibuprofen 400 mg powder for oral suspension (Spidifen®), b.i.d
Marketing authorisation holder:
ZAMBON ITALIA S.r.l., Via Lillo del Duca 10, 20091 Bresso (MI)
Batch number: 09B04/1
Daily dose: 1600 mg

Ibuprofen 400 mg powder for oral suspension (Spididol®)
Marketing authorisation holder:
ZAMBON ITALIA S.r.l., Via Lillo del Duca 10, 20091 Bresso (MI)
Batch number: 311736
Daily dose: 1600 mg

Duration of treatment: 14 days

Statistical Methods:

PRIMARY CRITERION - SAFETY
A one sided 97.5% confidence interval has been derived for the primary criterion (difference between test and reference for investigational medicinal product related gastrointestinal-

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event rate) proving non-inferiority by remaining below 0.08 with the upper interval limit (Statistical Software used: EquivTest (© 2008 Statistical Solutions)).

SECONDARY CRITERIA
Summarising statistics as well as confidence intervals are presented for measured and derived data (i.e. SPID).
Secondary criteria for tolerability as well as efficacy have been compared by confidence intervals for difference parameters of means or proportions, or using statistical tests depending on distribution and variable characteristics (t-test or Wilcoxon rank-sum test depending on normal distribution or Chi square test respectively), in accordance to appropriateness.

OBSERVATIONAL
Demographic and anamnestic data, also baseline data of laboratory examination, are presented based on summarising simple statistics for checking comparability of groups.

Criteria for evaluation:

Primary Criterion - Tolerability:
Investigational Medicinal Product Related Gastrointestinal Event Rate per Patient
Equivalence Parameter: Difference of Proportions
Equivalence Bound(s) [Upper]: 0.0800 (8%)
Alpha Value(s) [Upper]: 0.0250

	Yes	No	Total	Proportions	%
Dexibuprofen	8	232	240	0.0333	3.33
Ibuprofen	19	224	243	0.0782	7.82
Total	27	456	483	0.0559	5.59

IMP-related GI-events per patient

Statistic	Value
Difference of Proportions	-0.0448
Rate Ratio	0.4263
Odds Ratio	0.4065

Statistics IMP-related GI-events per patient

	Confidence Bounds Specified	Observed	Within Equivalence Limits?
Upper [2.50]% Conf. limit	0.0800	-0.0020	Yes

Confidence Interval based on Hauck-Anderson method for IMP-related GI-events per patient

The observed upper confidence limit of the one-sided 97.5% confidence interval for the difference (Dexibuprofen - Ibuprofen) in proportions of investigational medicinal product

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related gastrointestinal-events lies with (-0.002) clearly below the defined upper margin of 0.08. For that significant non-inferiority is shown.

Comparing both groups by Chi square test shows a significant lower proportion of IMP related GI events in the Dexibuprofen group, which is confirmed by the two-sided 95% confidence interval for the difference of proportions excluding zero and lying completely below zero (p = 0.032; 95% CI for difference of proportions: -0.0855 to -0.0042).

Secondary Criteria – Tolerability:

Investigational Medicinal Product Related Events per Patient

- Equivalence Parameter: Difference of Proportions
- Equivalence Bound(s) [Upper]: 0.0800 (8%)
- Alpha Value(s) [Upper]: 0.0250

	Yes	No	Total	Proportions	%
Dexibuprofen	21	219	240	0.0875	8.75
Ibuprofen	37	206	243	0.1523	15.23
Total	58	425	483	0.1201	12.01

IMP-related events (all SOC) per patient

Statistic	Value
Difference of Proportions	-0.0647
Rate Ratio	0.5747
Odds Ratio	0.5339

Descriptive Statistics IMP-related events (all SOC) per patient

	Confidence Bounds		
	Specified	Observed	Within Equivalence Limits?
Upper [2.50]% Conf. limit	0.0800	-0.0049	Yes

Confidence Interval based on Hauck-Anderson method for IMP-related events (all SOC) per patient

The observed upper confidence limit of the one-sided 97.5% confidence interval for the difference (Dexibuprofen - Ibuprofen) in proportions of investigational medicinal product related events lies with (-0.0049) clearly below the defined upper margin of 0.08. For that significant non-inferiority is shown.

Comparing both groups by Chi square test shows a significant lower proportion of IMP related events in the Dexibuprofen group, which is confirmed by the two-sided 95% confidence interval for the difference of proportions excluding zero and lying completely below zero (p = 0.028; 95% CI for difference of proportions: -0.1224 to -0.0072).

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Adverse Event Rate per Patient

- Equivalence Parameter: Difference of Proportions
- Equivalence Bound(s) [Upper]: 0.0800 (8%)
- Alpha Value(s) [Upper]: 0.0250

	Yes	No	Total	Proportions	%
Dexibuprofen	32	208	240	0.1333	13.33
Ibuprofen	54	189	243	0.2222	22.22
Total	86	397	483	0.1781	17.81

Adverse Event per patient

Statistic	Value
Difference of Proportions	-0.0888
Rate Ratio	0.6000
Odds Ratio	0.5385

Descriptive Statistics Adverse Event per patient

	Confidence Bounds		
	Specified	Observed	Within Equivalence Limits?
Upper [2.50]% Conf. limit	0.0800	-0.0189	Yes

Confidence Interval based on Hauck-Anderson method for Adverse Event per patient

The observed upper confidence limit of the one-sided 97.5% confidence interval for the difference (Dexibuprofen - Ibuprofen) in proportions of any adverse event lies with (-0.0189) clearly below the defined upper margin of 0.08. For that significant non-inferiority is shown.

Comparing both groups by Chi square test shows a significant lower proportion of any adverse event in the Dexibuprofen group, which is confirmed by the two-sided 95% confidence interval for the difference of proportions excluding zero and lying completely below zero (p = 0.010; 95% CI for difference of proportions: -0.1566 to -0.0212).

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Tolerability Assessment by Investigator and Patient (ITT)

		Group			
		Dexibuprofen		Ibuprofen	
		N	%	N	%
Tolerability Physician	very good	150	63,8%	126	53,6%
	good	57	24,3%	59	25,1%
	moderate	20	8,5%	21	8,9%
	unsatisfactory	3	1,3%	9	3,8%
	bad	5	2,1%	20	8,5%
Tolerability Patient	very good	143	60,9%	120	51,1%
	good	61	26,0%	63	26,8%
	moderate	19	8,1%	22	9,4%
	unsatisfactory	3	1,3%	9	3,8%
	bad	9	3,8%	21	8,9%

Tolerability of treatment assessed by physician and patient

Comparing the treatment-groups by Chi square test a significant difference could be found for the physician assessment ($p = 0.007$) as well as for the patient assessment ($p = 0.039$). Both results are indicating a significant shift to the rating "very good" for the Dexibuprofen group.

Secondary Criteria - Efficacy:

Pain Intensity Difference (ITT) – Visual Analogue Scale

The following table shows the results of the sum of pain intensity differences of the pain scales with reference to visit 2 (day 3) and final visit (day 14) for the ITT data set.

				95% CI of Mean Diff	
	Mean Diff	Median Diff	SE of Mean Diff	95% LB	95% UB
SPID night_V2	-1,67	-3,50	8,13	-17,65	14,32
SPID morn_V2	-8,34	-6,00	9,05	-26,12	9,44
SPID rest_V2	3,37	-5,00	8,54	-13,42	20,16
SPID motion_V2	-5,14	-6,00	8,72	-22,27	12,00
SPID night_final	17,53	-17,00	33,09	-47,49	82,56
SPID morn_final	2,46	-12,00	36,07	-68,43	73,34
SPID rest_final	25,91	12,50	32,88	-38,70	90,52
SPID motion_final	-51,99	-72,00	36,58	-123,87	19,89

Differences between treatment groups in SPID for day 3 (V2) and day 14 (final) – ITT; night=pain night, morn=pain morning, rest=pain at rest, motion=pain at motion

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All confidence intervals contain zero indicating no significant difference between the treatment groups.

Joint Pain/Quality of Life (ITT) – Verbal Rating Scale
The following table shows the results of the frequency count of the global pain (absolute and percent values) for the two treatment groups:

		Group			
		Dexibuprofen		Ibuprofen	
		N	%	N	%
Joint Pain BL	no	0	0,0%	0	0,0%
	mild	0	0,0%	0	0,0%
	moderate	87	36,3%	102	42,0%
	strong	133	55,4%	121	49,8%
	extreme	20	8,3%	20	8,2%
Joint Pain V2	no	6	2,6%	12	5,2%
	mild	71	30,6%	75	32,8%
	moderate	119	51,3%	109	47,6%
	strong	33	14,2%	31	13,5%
	extreme	3	1,3%	2	0,9%
Joint Pain final	no	19	8,1%	19	8,2%
	mild	87	37,0%	101	43,3%
	moderate	92	39,1%	70	30,0%
	strong	33	14,0%	40	17,2%
	extreme	4	1,7%	3	1,3%

Assessment of joint pain at baseline (BL), visit 2 (V2) and final visit (final)

Comparing the treatment-groups by Chi square test no significant difference could be found at any time point (Baseline p = 0.419; Visit 2 p = 0.593; final p = 0.305).
Similar shifts to no or mild joint pain after baseline could be observed for both treatment groups.

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Assessment of Condition of Health (ITT) – Verbal Rating Scale
The following table shows the results of the frequency count of condition of health (absolute and percent values) for the two treatment groups:

		Group			
		Dexibuprofen		Ibuprofen	
		N	%	N	%
Cond. .of Health BL	very good	21	8,8%	21	8,6%
	good	92	38,3%	85	35,0%
	satisfactory	81	33,8%	100	41,2%
	bad	39	16,3%	36	14,8%
	very bad	7	2,9%	1	0,4%
Cond. of Health V2	very good	19	8,2%	27	11,7%
	good	102	44,0%	92	40,0%
	satisfactory	91	39,2%	91	39,6%
	bad	18	7,8%	17	7,4%
	very bad	2	,9%	3	1,3%
Cond. of Health final	very good	26	11,1%	28	12,0%
	good	116	49,4%	115	49,1%
	satisfactory	66	28,1%	67	28,6%
	bad	21	8,9%	23	9,8%
	very bad	6	2,6%	1	0,4%

Assessment of condition of health at baseline (BL), visit 2 (V2) and final visit (final)

Comparing the treatment-groups by Chi square test no significant difference could be found at any time point (Baseline p = 0.143; Visit 2 p = 0.712; final p = 0.441).
Similar shifts to very good or good health condition after baseline could be observed for both treatment groups.

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Pain Relief (ITT)

The following table shows the results of the pain relief evaluation for the ITT data set with reference to visit 2 (day 3) and final visit (day14). The two treatment groups are displayed separately. Missing values are replaced by LVCF. The changes in pain relief have been calculated individually for each patient as time weighted sum.

			TOTPAR_V2	TOTPAR_final
Group	Dexibuprofen	Mean	4,65	23,52
		Median	4,00	24,00
		SD	4,01	15,39
		Min	0,00	0,00
		Max	20,00	60,00
		Q1	2,00	13,00
		Q3	8,00	37,00
		N	227	227
	Ibuprofen	Mean	4,63	23,80
		Median	4,00	24,00
		SD	4,10	16,11
		Min	0,00	0,00
		Max	21,00	77,00
		Q1	2,00	12,00
		Q3	8,00	36,00
		N	224	222

TOTPAR at visit 2 (V2) and final visit (final)

				95% CI of Mean Diff	
	Mean Diff	Median Diff	SE of Mean Diff	95% LB	95% UB
TOTPAR_V2	0,02	0,00	0,38	-0,73	0,77
TOTPAR_final	-0,28	0,00	1,49	-3,20	2,64

Differences between treatment groups in TOTPAR for day 3 (V2) and day 14 (final)

All confidence intervals contain the zero indicating no significant difference between groups. As confidence intervals are centering the zero value in a rather symmetric way, an equivalent situation for the compared groups can be concluded.

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Theoretical Maximum TOTPAR (ITT)

The following table shows the results of the theoretical maximum TOTPAR evaluation in percent for the ITT data set. The two treatment groups are displayed separately.

			TMT
Group	Dexibuprofen	Mean	41,50
		Median	44,64
		SD	26,10
		Min	0,00
		Max	100,00
		Q1	25,00
		Q3	65,00
		N	227
	Ibuprofen	Mean	42,03
		Median	43,30
		SD	26,67
		Min	0,00
		Max	96,43
		Q1	21,88
		Q3	67,31
		N	222

TMT (%) for both treatment groups

				95% CI of Mean Diff	
	Mean Diff	Median Diff	SE of Mean Diff	95% LB	95% UB
TMT (%)	-0,53	1,34	2,49	-5,42	4,37

Differences between treatment groups in TMT (%)

Confidence interval contains the zero indicating no significant difference between groups.

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TMT-Responders (TMT≥50%) (ITT)
The following tables show the results of the TMT-Responders ≥ 50% in percent for the ITT data set. The two treatment groups are displayed separately.

		TMT_Resp			
		Yes		No	
		N	%	N	%
Group	Dexibuprofen	102	44,9%	125	55,1%
	Ibuprofen	98	44,1%	124	55,9%

TMT ≥ 50% Responders at final visit (day 14)

Responders			CI of Resp. Diff	
Dexibuprofen	Ibuprofen	CI Level	LB	UB
44,9%	44,1%	90%	-0,069	0,085
		95%	-0,084	0,099
		99%	-0,113	0,128

Confidence intervals for the TMT ≥ 50% responder-difference

Confidence intervals contain the zero indicating no significant difference between groups. All intervals show a symmetric shape around zero indicating equivalent situations in compared groups.

Efficacy Assessment by investigator and patient (ITT)

		Group			
		Dexibuprofen		Ibuprofen	
		N	%	N	%
Efficacy Physician	very good	61	48,0%	55	42,0%
	good	31	24,4%	37	28,2%
	moderate	20	15,7%	27	20,6%
	unsatisfactory	11	8,7%	5	3,8%
	bad	4	3,1%	7	5,3%
Efficacy Patient	very good	50	39,4%	43	32,8%
	good	30	23,6%	39	29,8%
	moderate	30	23,6%	36	27,5%
	unsatisfactory	11	8,7%	5	3,8%
	bad	6	4,7%	8	6,1%

Efficacy of treatment assessed by physician and patient

Comparing the treatment-groups by Chi square test there was neither a significant difference for the physician assessment ($p = 0.627$) nor for the patient assessment ($p = 0.795$) to be found.

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SUMMARY – CONCLUSION:

SAFETY RESULTS:

The observed upper confidence limit of the one-sided 97.5% confidence interval for the difference (Dexibuprofen - Ibuprofen) in proportions of IMP related gastrointestinal (GI) events per patient lies with (-0.002) clearly below the defined upper margin of 0.08. For that significant non-inferiority is shown.

Comparing both groups by Chi square test shows a significant lower proportion of IMP related GI events per patient in the Dexibuprofen group, which is confirmed by the two-sided 95% confidence interval for the difference of proportions lying completely below zero (p = 0.032; 95% CI for difference of proportions: -0.0855 to -0.0042).

The observed upper confidence limit of the one-sided 97.5% confidence interval for the difference (Dexibuprofen - Ibuprofen) in proportions of IMP related events (all SOC) per patient lies with (-0.0049) clearly below the defined upper margin of 0.08. For that significant non-inferiority is shown.

Comparing both groups by Chi square test shows a significant lower proportion of IMP related events (all SOC) per patient in the Dexibuprofen group, which is confirmed by the two-sided 95% confidence interval for the difference of proportions lying completely below zero (p = 0.028; 95% CI for difference of proportions: -0.1224 to -0.0072).

The observed upper confidence limit of the one-sided 97.5% confidence interval for the difference (Dexibuprofen - Ibuprofen) in proportions of any adverse event per patient lies with (-0.0189) clearly below the defined upper margin of 0.08. For that significant non-inferiority is shown.

Comparing both groups by Chi square test shows a significant lower proportion of any adverse event per patient in the Dexibuprofen group, which is confirmed by the two-sided 95% confidence interval for the difference of proportions lying completely below zero (p = 0.010; 95% CI for difference of proportions: -0.1566 to -0.0212).

Comparing the treatment-groups for tolerability by Chi square test a significant difference can be found for the physician assessment (p = 0.007) as well as for the patient assessment (p = 0.039) in the ITT population. Both results are indicating a significant shift to the rating "very good" for the Dexibuprofen group. In the PP population shifts were similar but the difference was not significant anymore.

In summary safety analyses revealed at least non-inferiority for the Dexibuprofen group.

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EFFICACY RESULTS:
For the calculated parameter "Sum of Pain Difference (SPID)" all confidence intervals at any time point (day 3; day 14) for any situation (morning, night, rest, motion) contain zero, indicating no significant difference between groups for the ITT population. For the PP population the situation was equal, except for the mean difference in motion at 14 days. Here the complete confidence interval is below zero suggesting a significantly stronger pain-reduction in the Dexibuprofen treatment group.

For "Total Pain Relief (TOTPAR)" all confidence intervals (day 3; day 14) contain zero indicating no significant difference between groups in both populations (ITT; PP). As confidence intervals centers zero in a rather symmetric way, an equivalent situation for the compared groups can be concluded.

For the parameters "Theoretical Maximum TOTPAR (%TMT)" and "Pain Relief Responders (%TMT >= 50%)" confidence intervals for difference in both populations (ITT; PP) contain zero indicating no significant difference between treatment groups.

For global subjective judgements for efficacy compared by Chi square test, neither a significant difference for the physician assessment nor for the patient assessment in any population (ITT; PP) was shown.

For joint pain and condition of health the comparison via Chi square test showed no significant difference at any visit or in any population (ITT; PP).

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