Sponsor code CHL1/02-2006/M
(CRO code INN60M2006)
EudraCT number 2007-000968-25

Prospective, blind-observer, randomised clinical study to investigate and compare the efficacy of intrathecal plain solutions containing Chloroprocaine 1% (50 mg) versus Bupivacaine 0.5% (10mg)

Prospective, blind-observer, randomised, multicentre study

Test formulation(s):	Chloroprocaine 1% , Sintetica S.A.
Reference formulation(s):	Bupivacaine 0.5% (10 mg), AstraZeneca
Sponsor:	Sintetica S.A. - Via Penate 5, CH-6850 Mendrisio, Switzerland Phone: +41.91.640.42.50 Fax: +41.91.646.85.61 Email: info@sintetica.com Sintetica Italia Srl – Piazza della Repubblica 25, I-20121 Milano Phone: +39.02.654.747 Fax: +39.02.654.724 Email: italia@sintetica.com
Investigator(s):	Guido Fanelli MD - (Coordinating Investigator) Azienda Ospedaliera di Parma – Università di Parma –Dipartimento di Anestesia, Rianimazione e Terapia Antalgica - via Gramsci, 14, I-43100 Parma, Italy Tel: +39 0521 702 159 Fax: +39 0521 702 733 e-mail: g.fanelli@ao.pr.it
Development phase:	Phase III
First subject enrolled	07.09.2007
Last subject completed	19.11.2008
Version and date:	Final version, 09 April 09

This study was conducted in accordance with Good Clinical Practice (GCP) and with ICH topic E6

This document comprises 71 pages plus appendices

1 FINAL REPORT APPROVAL PAGE

Protocol Code: *CHL1/02-2006/M*

Report title: **Prospective, blind-observer, randomised clinical study to investigate and compare the efficacy of intrathecal plain solutions containing Chloroprocaine 1% (50 mg) versus Bupivacaine 0.5% (10mg)**

09/04/09
Date (dd/mm/yy)

Alessandra Bertani
Author

Signature

09 APR./2009
Date (dd/mm/yy)

Prof. Guido Fanelli
Coordinating Investigator

Signature

08/04/09
Date (dd/mm/yy)

Elisabetta Donati
Study Co-ordinator

Signature

08/04/2009
Date (dd/mm/yy)

Barbara Riccardi.
Q.A. Manager

Signature

2 SYNOPSIS

Name of Company: Sintetica S.A., Switzerland	**TABULAR FORMAT**			**(For National Authority Use only)**
Name of Finished Product: Chloroprocaine 1%	**REFERRING TO PART OF THE DOSSIER**		5.3	
Name of active substance(s):	**Volume:**			
Chloroprocaine hydrochloride	**Page:**			

Title of the study:
Prospective, blind-observer, randomised clinical study to investigate and compare the efficacy of intrathecal plain solutions containing Chloroprocaine 1% (50 mg) versus Bupivacaine 0.5% (10 mg)

Study Centres and Principal Investigator(s):

1. University Hospital of Parma (co-ordinator site),Via Gramsci, 14 I-43100 Parma, Italy, Guido Fanelli, MD

2. University Hospital Giessen and Marburg Baldingerstraße D-35043 Marburg, Germany, Hinnerk Wulf, MD

3. Ospedale Regionale di Lugano, Via Tesserete, 46 CH-6903 Lugano, Switzerland, Claudio Camponovo, MD

Publication (reference):

Studied period (years):	**Date of first enrolment:** 07SEP07	**Phase of development:**
2007-2008	**Date last visit completed:** 19NOV08	**III**

Objectives:
To compare the performance of 50 mg of Chloroprocaine 1% in intrathecal anaesthesia vs. a gold standard product 10 mg of Bupivacaine 0.5%

Methodology:
prospective, blind-observer, randomised, multicentre study

Number of subjects (planned and analysed):
120 subjects undergoing elective short-duration (< 40 min) in low abdominal surgery (gynaecology and urology disciplines) that required T10 metameric level of sensory block and identical anaesthesia procedures

Diagnosis and criteria for inclusion:
male/female subjects scheduled for low abdominal surgery (gynaecology and urology disciplines) (less than 40 min) that required T10 metameric level of sensory block and identical anaesthesia procedures, 18-80 years old; 18≤BMI≤32 kg/m2; physical status ASA I-II according to the American Society of Anaesthesiologists; no clinically relevant abnormal physical findings and no clinically relevant abnormal laboratory values indicative of physical illness/es that in the opinion of the Investigator might interfere with the aim of the study; no ascertained or presumptive hypersensitivity to the active principle and/or formulations ingredients; no ascertained or presumptive hypersensitivity to the amide type of anaesthetics and/or to major anaesthetics; no ASA physical status III-V; not subjects requiring further anaesthesia (i.e. gas products); not lactating females; no pregnant women; contraindications to spinal anaesthesia, sepsis, blood coagulation disorders, ascertained psychiatric or neurological diseases; no treatment with opioids; no participation in the evaluation of any drug within 3 months prior to screening; no blood donations during the 3 months prior to this study; no history of drug, or alcohol abuse; ability to comprehend the full nature and purpose of the study, including possible risks and side effects; ability to co-operate with the Investigator and to comply with the requirements of the entire study; signed written informed consent prior to inclusion in the study

Test product, dose, mode of administration, batch N°:
Plain Chloroprocaine, Sintetica S.A., containing Chloroprocaine hydrochloride 1%, 5 mL corresponding to 50 mg of Chloroprocaine was injected once as an intrathecal injection;
Batch: 06170; Expiry date: SEP09

SYNOPSIS (cont.)

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Chloroprocaine hydrochloride	Page:		

Reference therapy, dose, mode of administration, batch N°:
Bupivacaine Astra Zeneca containing Bupivacaine 0.5%, 2 mL corresponding to 10 mg of Bupivacaine were injected once as an intrathecal injection;
Batch: HK1127A3; Expiry date: OCT11

Criteria for evaluation (efficacy):
- Time to onset to sensory block at T10;
- Time to onset to motor block; the level of motor block is assessed by using the modified Bromage's scale
- Maximum level of sensory block
- Resolution (Offset) of sensory block to S1
- Resolution of motor block (Bromage score = 0)
- Time to unassisted ambulation
- Presence of urinary retention
- Time when subject asks the first time for analgesia
- Time to eligibility for home discharge (for day surgery only)

Criteria for evaluation (safety):
AEs, cardiovascular AEs; ECG abnormalities, BP, HR, SpO2, Transient Neurological Symptoms TNS

Statistical methods:
Individual data were to be listed. Classic descriptive statistics (n, mean, standard deviation, CV%, minimum and maximum) were to be presented for quantitative parameters and table of frequencies for the qualitative ones.

For the primary end-point parameter the following hypotheses were to be considered: H_0: $\mu_{\text{time of onset to T10, reference}} - \mu_{\text{time of onset to T10, test formulation}} > 4$ min, vs. the alternative hypothesis: H_1: $\mu_{\text{time of onset to T10, reference}} - \mu_{\text{time of onset to T10, test formulation}} \leq 4$ min

Independent samples T-test were to be used with significance level α 5% two-sided. In case of lack of normality of the underlying distributions, the Wilcoxon rank-sum test will be used instead.

The null hypothesis were to be tested by constructing the 95% confidence interval for the difference between the two mean times of sensory block to T10 ($\mu_{\text{time of onset to T10, reference}} - \mu_{\text{time of onset to T10, test formulation}}$): the upper limit of the confidence interval was to be compared with the non-inferiority limit of 4 min; this is equivalent to a one-sided 0.025 test. In case of lack of normality of the underlying distributions, non parametric methodology was to be used instead.

For the secondary end-point parameters, comparison of test vs. reference group was to be performed for all quantitative primary and secondary end-points by independent samples T-tests or non parametric equivalents, when more appropriate. For qualitative parameters, Chi-square tests were to be applied, when appropriate. Tests were to be two-sided at 5% significance level.

Results:
The following table summarises minimum, median and maximum time, in minutes, for achieving sensory block at T10, for achieving motor block (Bromage's score ≥ 2) for complete spinal block resolution, recovery of unassisted ambulation, and home discharge after intrathecal injection of 50 mg Chloroprocaine (T), and 10 mg (R) of Bupivacaine.

	T onset sensory block			T onset motor block			T end of anaesthesia			T unassisted ambulation			T home discharge		
	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max
T	1.0	7.9	30.0	1.0	5.7	26.0	60.0	109.2	194.0	86.0	163.3	454.0	90.0	190.3	454.0
R	1.0	9.4	27.0	1.0	7.6	27.0	130.0	235.5	442.0	190.0	307.4	490.0	190.0	324.1	490.0

SYNOPSIS (cont.)

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Results (cont.):

Significant difference ($p<0.05$) was detected between T and R for that concerns time to achieve motor block, maximum level of sensory block, end of anaesthesia, unassisted ambulation and eligibility for home discharge. Moreover significant difference was detected between the two treatments for all the other considered parameters (non parametric test).
A total of 20 Adverse Events, 13 in the reference group, involving 8 (12.5%) subjects, and 7 in test group, involving 7 subjects (10.6%) were reported. Out of them, 11 in the reference group and 4 in the test group were judged as related to study treatment. Out of the 3 observed SAE, none was related to study drug.

Conclusions: intrathecal local anaesthesia induced with 50 mg 1% 2-Chloroprocaine provided adequate spinal anaesthesia for low abdomen and lower limb surgery procedures lasting less than 40 minutes with significant quicker achievement of surgical anaesthesia and a quicker recovery from anaesthesia and eligibility for home discharge respect to 10 mg 0.5% Bupivacaine. Moreover safety profile of 50 mg Chloroprocaine 1% seems to be more favourable respect to reference treatment.

Date of the report: final version, 09APR09