Integrated Clinical Trial Report Synopsis

Extension of:

A randomised, parallel-group, open, controlled Phase III trial assessing the treatment compliance with Grazax® in subjects with seasonal grass pollen induced rhinoconjunctivitis
Investigational Medicinal Product: Grazax

Clinical trial ID:	GT-10 Extension
EudraCT No.	2005-004724-39
Indication:	Seasonal grass pollen induced rhinoconjunctivitis
Development Phase:	III
First subject first visit:	28 August 2006
Last subject last visit:	21 November 2007
Investigators:	34 investigators in Denmark, Germany, The Netherlands and Sweden. *Signatory Investigator*: [redacted] MD, Sweden
Trial centres:	32 centres in Denmark, Germany, The Netherlands and Sweden
Sponsor:	Group Clinical Development ALK-Abelló A/S DK-2970 Hørsholm, Denmark
Clinical Trial Manager:	[redacted] MSc. Pharm, ALK-Abelló A/S
Report No. and date:	GT-10 Extension, 2008, final, 23 June 2008

This trial was conducted in compliance with the principles of *ICH Good Clinical Practice*.

Synopsis – GT-10 Extension

Title of Trial

Extension of: A randomised, parallel-group, open, controlled Phase III trial assessing the treatment compliance with Grazax® in subjects with seasonal grass pollen induced rhinoconjunctivitis

Investigators

34 investigators in Denmark, Germany, The Netherlands, and Sweden

Trial Centres

32 centres in Denmark, Germany, The Netherlands, and Sweden

Publication

None

Trial Period

First subject first visit (of GT-10 extension) – 28 August 2006

Last subject last visit (of GT-10 extension) – 21 November 2007

Objectives

The GT-10 Extension was implemented by General Amendment 2 (dated 20-June-2006) to the GT-10 trial protocol. In accordance with the GT-10 protocol, section 9.6, Post-Trial Treatment, and the Declaration of Helsinki, the subjects in the GT-10 trial was offered Grazax treatment until a Marketing Authorisation had been obtained and the product was available on the market in the individual countries **or** for a maximum of one year, whichever came first.

Evaluations comprised compliance, global evaluation (for subjects who were treated throughout the 2007 grass pollen season) and safety (adverse events) of Grazax treatment.

Methodology

The GT-10 trial was a randomised, parallel group, open, controlled, multi-centre trial. The trial was initiated in February 2006 and subjects received Grazax for approximately 6-12 weeks prior to the grass pollen season and during the grass pollen season 2006. Approximately 500 subjects were planned for inclusion in the trial. The subjects were randomised (1:1) and 250 subjects would receive a compliance device (Memozax) and 250 would not. All subjects received Grazax. In the GT-10 Extension, all subjects that completed GT-10 were offered the use of the Memozax compliance device. The duration of treatment in the GT-10 Extension trial varied between countries, and depended on when Grazax became commercially available in each country.

The following visits and procedures were scheduled for the GT-10 Extension trial period:

Visit	**3** *End of Trial (Start of Extension Treatment)*	**4** *Oct./Nov. 2006*	**5** *Jan./Feb. 2007*	**6** *April/May 2007*	**7** *End of Follow-up*
Time	*Approx 2 weeks after the end of the grass pollen season 2006*				*After the end of the grass pollen season 2007*
Informed consent (Extension Treatment)	X				
Assessment of adverse events	X	X	X	X	X
Dispensing of Grazax	X	X	X	X	
Collection of Grazax – Drug accountability	X	X	X	X	X

Number of Subjects Planned and Analysed

500 subjects were planned for inclusion in the GT-10 trial. A total of 460 subjects enrolled in the trial and 240 of them were randomised to receive the Memozax device. Of the 380 subjects that completed the GT-10 trial, 264 subjects chose to continue in the GT-10 Extension.

Treatment Group	GRAZAX + Memozax N	(%)	GRAZAX - Memozax N	(%)	Overall GRAZAX N	(%)
GT-10						
Screened					472	
Full Analysis Set #	240	(100%)	220	(100%)	460	(100%)
Subjects withdrawn	36	(15%)	44	(20%)	80	(17%)
Subjects completed	204	(85%)	176	(80%)	380	(83%)
GT-10 Extension						
Subjects enrolled					264	(100%)
Subjects withdrawn					38	(14%)
Subjects completed					226	(86%)
Reason for Withdrawal						
Adverse event					7	(3%)
Withdrawal of consent					7	(3%)
Lost to follow-up					12	(5%)
Non-Compliance with Protocol					5	(2%)
Other					7	(3%)

N = Number of subjects; % = Percent subjects

Full Analysis Set comprises all randomised subjects

38 subjects (14%) withdrew from the trial during the Extension period. The main reason for withdrawals was Lost to-follow-up, and most withdrawals were initiated by the subjects themselves.

Diagnosis and Main Inclusion Criteria

Subjects suffering from grass pollen induced rhinoconjunctivitis with or without asthma were eligible for the GT-10 trial. Subjects with a clinical history of severe asthma during the last two grass pollen seasons and/or a history of emergency visit or admission for asthma in the previous 12 months and/or $FEV_1 < 70\%$ of predicted value at randomisation were excluded.

The GT-10 Extension trial enrolled subjects who had completed the GT-10 trial, gave informed consent, and who, in agreement with the investigator, were likely to benefit from continued treatment with Grazax.

Investigational Medicinal Product, Dose and Mode of Administration, Batch Number

Grazax – 75,000 SQ-T; sublingual administration, batch Nos. 382250 (dispensed to all subjects at visits 3 and 4) and 456440 (dispensed to all subjects at visits 5 and 6).

Reference Therapy, Dose and Mode of Administration, Batch Number(s)

None

Duration of Treatment

Up to one year, depending on when Grazax became commercially available in the respective countries.

Subjects in DK were treated for approximately 12 months, subjects in DE for approximately 3 months, subjects in SE for approximately 6 months, and subjects in NL for approximately 10 months.

Criteria for Evaluation – Compliance and Efficacy

- Global evaluation (for subjects who were treated throughout the 2007 grass pollen season)

Criteria for Evaluation – Safety

Adverse events (AEs)

Statistical Methods

The following analysis set was used:

- Full-analysis set (FAS) – all subjects continuing in the Extension part

Efficacy Endpoints

Only summary statistics were used to evaluate the results.

Safety Endpoints

Only descriptive statistics were used to evaluate the adverse events. Adverse events were tabulated and listed.

Demography of Trial Population

The mean age of subjects included in the Extension was 37 years (overall range 19 to 67 years of age) and 130 (49%) subjects were male. Of the 264 subjects included in the GT-10 extension, 36 were from Denmark, 79 were from Germany, 50 were from The Netherlands and 99 were from Sweden.

Efficacy Results

The first season with Grazax treatment (original GT-10 trial) resulted in 82% of subjects rating their rhinoconjuctivitis symptoms as Improved compared to previous seasons. In addition to the improvement in the first season, 81% (34 out of 42 subjects) of subjects also rated their rhinoconjunctivitis symptoms as Improved during the second season as compared to previous seasons. In total, 40 of the 42 subjects improved in both the first and the second season or in either the first or the second season, while only 2 subjects did not improve in either the first or the second season.

The primary endpoint in the original GT-10 trial (compliance) was not assessed in the GT-10 extension as all subjects in the extension part of the trial were offered the compliance device Memozax.

Safety Results

This trial documented the safety of Grazax after a longer period of exposure to the product. Subjects had been exposed for 6-12 weeks prior to and during the grass pollen season 2006 before entering the extension part of the GT-10 trial.

- Overall 73 (28%) of the 264 subjects randomised reported a total of 115 TEAEs during the GT-10 extension trial. 31 of the 115 events were judged as possibly or probably related to IMP treatment. 57 subjects reported mild events (23 with IMP related mild events), 25 reported moderate events (5 with IMP related moderate events), and 5 subjects reported severe events (none were related to IMP).
- Of the related TEAEs, oral pruritus was the most common (11 subjects with a total of 12 events), followed by throat irritation (3 subjects with a total of 3 events), ear pruritus (2 subjects with a total of 2 events), eye pruritus (2 subjects with a total of 2 events), and gastritis (2 subjects with a total of 2 events).
- No single adverse event occurred in ≥5% of the trial subjects during the GT-10 extension trial.
- 2 subjects (0.8%) had SAEs but both of the events were judged unlikely related to IMP treatment (hysterectomy and gallbladder disorder).
- 7 subjects (3%) withdrew from the trial due to an AE. Adverse events leading to withdrawal were: Gastritis (n=1), Oral pruritus (n=1), Chest discomfort and Respiratory tract infection (n=1), Chronic sinusitis (n=1), Maxillary sinusitis (n=1), Rhinitis allergic (n=1), Eczema (n=1).

Conclusions

Grazax was generally well tolerated by the subjects in this trial. No safety concerns were identified for subjects treated with Grazax over a longer period of time.

Date of the Synopsis

Final, 23 June 2008

This trial was conducted in compliance with the principles of *ICH Good Clinical Practice*.