2 SYNOPSIS

Name of Sponsor/Company: Bionorica SE Name of Finished Product: - Name of Active Ingredient: Galphimia glauca dry extract BNO 1355	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use only)

EudraCT no.	2010-018786-33
Study code	AlRhi-IIa
Title of study	A randomized, double-blind, placebo-controlled, cross-over phase IIa/b study to assess the efficacy and safety of two dosages of a herbal medicinal product (dry extract BNO 1355) in subjects with seasonal allergic rhinitis
Study design	Single centre, randomized, double-blind, placebo-controlled, three-period, cross-over study.
Phase of development	IIa/b
Principal investigator (LKP according to §40 German Drug Law)	[redacted]
Investigators	[redacted]
Study centre(s)	One
Country	Germany
Publication (reference)	None
Studied period	Approx. 4 months (clinical part) Date of first enrolment (first subject first visit) 24 AUG 2010 Date of last completed (last subject last visit) 04 JAN 2011
Objectives	To assess both the acute and the prophylactic effect of two different dosages of BNO-1355 in seasonal allergic rhinitis compared to placebo in an environmental challenge chamber (ECC)
Study visits	The study comprised a screening phase of up to 28 days with two visits (Visit 1 – Visit 2), a three-way-cross-over treatment phase of at least 52 days with 6 visits (Visit 3 – Visit 8), and one follow-up visit (Visit 9) scheduled 1 to 7 days after the end of the treatment phase.
Methodology	Male and female adult subjects with seasonal allergic rhinitis who were currently free of symptoms were screened for study participation from AUG 2010 to JAN 2011 (late summer-winter). The maximum individual study duration was approx. 12 weeks (87 days) with 9 visits to the study site and one brief check-up on the day after the screening allergen challenge done at Visit 2. Allergic rhinitis was confirmed by positive skin prick test to Dactylis glomerata and a Total Nasal Symptom Score (TNSS) score of ≥6 at least once during the 2-hour baseline exposure to Dactylis glomerata in an environmental challenge chamber (ECC) at Visit 2 (screening allergen challenge). The treatment phase consisted of three blinded treatment periods each lasting for 8 days: Period 1 (Visit 3-Visit 4), Period 2 (Visit 5-Visit 6), Period 3 (Visit 7-Visit 8). There were two wash-out periods of minimum 14 days between treatments. The three investigational treatments (100 mg BNO 1355, 200 mg BNO 1355 and placebo) were administered in six different sequence-arms. At Visit 3 (Day 1 of Period 1), subjects were allocated in a double-blinded manner and at random to one treatment sequence (randomization ratio: 1:1:1:1:1:1; i.e. 9 subjects per sequence-arm).

Name of Sponsor/Company: Bionorica SE	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: -	Volume:	
Name of Active Ingredient: Galphimia glauca dry extract BNO 1355	Page:	

Methodology (continued)	The blinded Investigational Medicinal Product (IMP) was administered three times a day (tid) during each of the three 8-day treatment periods (2 tablets tid = 6 tablets per day). First administration was 1h before allergen challenge on Day 1 of each period. Last administration was 1h before allergen challenge on Day 8 of each period. A subject diary was used to document drug administration at home and the need for rescue medication (Aerodur®Turbohaler) during each treatment period (Period 1, Period 2 and Period 3). Allergen challenge with Dactylis glomerata was used to evaluate the acute and the prophylactic effect of two dosages of BNO 1355 in seasonal allergic rhinitis compared to placebo. On Day 1 (Visit 3, Visit 5, Visit 7) and Day 8 (Visit 4, Visit 6, Visit 8) of each treatment period, subjects were exposed to pollen of Dactylis glomerata at a concentration of approximately 4000 grains per cubic meter in the ECC for 4 hours. Allergen challenge started one hour after drug administration on Day 1 and Day 8, respectively (drug administration under supervision of site staff). Subject's nasal allergic response was evaluated during the 4-hour allergen challenge by counting sneezes (subject's continuous recording for 4 hours with a manual counter), monitoring of four major nasal allergy symtoms (rating questionnaire completed by the subject every 20 minutes), measurement of nasal flow rate (rhinomanometry at hourly intervals) and extent of nasal secretion (weighing of used tissues every 60 minutes during the 4-hour allergen challenge). Subject's ratings of four major nasal allergy symtoms recorded in the questionnaire (4-point-verbal rating scale) were used to calculate the Total Nasal Symptom Score – TNSS (summation of scores for nasal congestion, rhinorrhea, nasal itching and sneezing). Safety and tolerability of study treatment was evaluated based upon adverse event monitoring (Visit 2-Visit 9), measurement of lung function (spirometry: Visit 1-Visit 9) and vital signs (blood pressure, pulse rate: Visit 1 and Visit 3-Visit 9), as well as safety laboratory tests (haematology, clinical chemistry, urinalysis: Visit 1 and Visit 3-Visit 9). Further safety measures included a pre/post-treatment physical examination with 12–lead electrocardiogram (Visit 1 and Visit 9), and continuing review of concomitant medication (Visit 1-Visit 9) including application of rescue medication (Visit 3-Visit 8). Female subjects of childbearing potential had to have a negative urine pregnancy test at each study visit (Visit 1-Visit 9).
Number of subjects	Planned: 54 subjects ; randomised: 54 subjects (overall SEP); analysed for 100 mg BNO 1355, 200 mg BNO 1355 and placebo - in the safety evaluable population (SEP): 49, 50 and 50 subjects, respectively - in the full analysis set (FAS) on Day 1/Day 8: 46/45, 47/46 and 47/45 subjects, respectively - in the per protocol set (PP) on Day 1/Day 8: 42/40, 42/40 and 44/41 subjects, respectively
Inclusion diagnosis	Seasonal allergic rhinitis, known for at least 2 years
Main criteria for inclusion	1. Signed informed consent including data protection declaration 2. Male or female outsubjects aged ≥18 and ≤65 years 3. Minimum 2 years history of seasonal allergic rhinitis 4. Positive skin prick test to Dactylis glomerata within 12 months prior to or on Visit 1 5. TNSS score of ≥6 at least once during the 2h-baseline ECC exposure 6. FEV1 ≥80 % predicted (ESCS)* at screening 7. A non-smoker for at least the past 12 months with a pack history of <10 pack years Pack years = (Number cigarettes smoked per day /20) x number of years smoked 8. Body Mass Index (BMI) ≥18 and ≤35

Name of Sponsor/Company: Bionorica SE	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: -	Volume:	
Name of Active Ingredient: Galphimia glauca dry extract BNO 1355	Page:	

Main criteria for inclusion (continued)	9. Women were considered for inclusion if they were: – not pregnant, as confirmed by pregnancy test and not nursing – of non-child bearing potential – of childbearing potential and using a highly effective method of contraception during the entire study * FEV1 ≥80 % of the predicted value given by prediction equations from the European Society for Coal and Steel (ESCS)
Investigational medicinal products (IMP)	
Test product	BNO 1355 coated tablet (CT)
Active ingredient(s)	one CT contained 100 mg dry extract BNO 1355
Mode of administration	peroral
Batch number:	0000043586 (blinded batch no. 0000045335)
Expiry date:	03/2012
Dose regimen of Dose 1 (100 mg) - Treatment A:	Day 1: 1x100 mg BNO 1355 CT plus 1 placebo CT in the morning and in the evening = 200 mg/day Day 2-Day 7: 1x100 mg BNO 1355 CT plus 1 placebo CT tid = 300 mg/day Day 8: 1x100 mg BNO 1355 CT plus 1 placebo CT once in the morning = 100 mg/day
Dose regimen of Dose 2 (200 mg) - Treatment B:	Day 1: 2x100 mg BNO 1355 CT in the morning and in the evening = 400 mg/day Day 2-Day 7: 2x100 mg BNO 1355 CT tid = 600 mg/day Day 8: 2x100 mg BNO 1355 CT once in the morning = 200 mg/day
Reference	Placebo coated tablet (CT)
Active ingredient(s)	None
Mode of administration	peroral
Batch number:	0000043587 (blinded batch no. 0000045335)
Expiry date:	03/2012
Dose regimen – Treatment C	Day 1: 2 placebo CT in the morning and in the evening = 4 CT/day Day 2-Day 7: 2 placebo CT tid = 6 CT/day Day 8: 2 placebo CT once in the morning = 2 CT/day
Sequential treatment	Each subject received sequential treatment with BNO 1355 at two dose levels (100 mg and 200 mg) and placebo.The three investigational treatments were administered in six different sequence-arms (table below gives the strength of one dose = 2 tablets):

Sequence-arm	Period 1 (8 days)	Period 2 (8 days)	Period 3 (8 days)
A	200 mg BNO 1355	Placebo	100 mg BNO 1355*
B	200 mg BNO 1355	100 mg BNO 1355*	Placebo
C	100 mg BNO 1355*	200 mg BNO 1355	Placebo
D	100 mg BNO 1355*	Placebo	200 mg BNO 1355
E	Placebo	200 mg BNO 1355	100 mg BNO 1355*
F	Placebo	100 mg BNO 1355*	200 mg BNO 1355

* plus placebo (double-dummy technique)

Randomization ratio between the six sequence-arms was 1:1:1:1:1:1, i.e. 9 subjects were assigned to each sequence-arm.

Name of Sponsor/Company: Bionorica SE	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: -	Volume:	
Name of Active Ingredient: Galphimia glauca dry extract BNO 1355	Page:	

Duration of treatment:	The three-way-cross-over treatment phase consisted of three blinded treatment periods (each lasting for 8 days) with two intervening wash-out periods (minimum 14 days each). Total duration of investigational treatment: 24 days.
Criteria for evaluation - Efficacy	PRIMARY EFFICACY ENDPOINTS (primary outcome measures) The primary efficacy variable was the Total Nasal Symptom Score (TNSS) triggered by allergen challenge. ▪ 1st primary endpoint The mean of the TNSS triggered by allergen challenge for the interval of 2-4 hours after start of the allergen challenge on Day 1 (Period 1, Period 2, Period 3) after first dose administration (100 mg BNO 1355, 200 mg BNO1355 or placebo) was chosen as primary endpoint to evaluate the **acute effect** of study treatments. ▪ 2nd primary endpoint The mean of the TNSS triggered by allergen challenge for the interval of 2-4 hours after start of the allergen challenge on Day 8 (Period 1, Period 2, Period 3) after 7 days treatment (100 mg BNO 1355, 200 mg BNO1355 or placebo) was chosen as primary endpoint to evaluate the **prophylactic effect** of study treatments. SECONDARY EFFICACY ENDPOINTS 1. The mean of the TNSS triggered by allergen challenge for the interval of 0-2 hours after start of the allergen challenge on Day 1 (acute treatment effect) and Day 8 (prophylactic treatment effect) 2. The maximum symptom intensity measured as TNSS triggered by allergen challenge calculated as score points on Day 1 (acute treatment effect) and Day 8 (prophylactic treatment effect) 3. Relative change from baseline in nasal flow rate (measured by rhinomanometry) 2 hours after start of the allergen challenge on Day 1 (acute treatment effect) and Day 8 (prophylactic treatment effect) 4. The maximum decrease in nasal flow rate (measured by rhinomanometry) triggered by allergen challenge relative to baseline on Day 1 (acute treatment effect) and Day 8 (prophylactic treatment effect) 5. The extent of nasal secretion (measured by weighing of used handkerchiefs) for the time interval of allergen challenge on Day 1 (acute treatment effect) and Day 8 (prophylactic treatment effect). 6. The number of sneezes during allergen challenge on Day 1 (acute treatment effect) and Day 8 (prophylactic treatment effect)
- Safety	1. Frequency and intensity of adverse events 2. Vital signs (blood pressure, pulse) 3. Lung function (measured by spirometry) 4. Safety laboratory

Name of Sponsor/Company: Bionorica SE	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: -	Volume:	
Name of Active Ingredient: Galphimia glauca dry extract BNO 1355	Page:	

Statistical method	The analyses of the primary and secondary endpoints were performed using the full analysis set (FAS) which included all randomized subjects with allergic rhinitis and with at least one documented application of the investigational drug and post-baseline effect data. The analysis of the per-protocol set (PP) was performed additionally as a sensitivity analysis to determine the effects of the subjects excluded from the PP cohort. All secondary data were analysed exploratively by descriptive statistics. Categorical variables were described in contingency tables as absolute numbers and percentages.
Statistical method (continued)	Differences between each dosage group of BNO 1355 (100 mg, 200 mg) and placebo regarding primary and secondary endpoints were analysed by analysis of variance (ANOVA) in order to adjust for period effects. Residual effects were not considered. For baseline adjustments, the analysis of covariance (ANCOVA) with "baseline" as covariate was used.

Summary – Conclusions: Efficacy results

Table 1 shows the mean values and standard deviations (SD) for the four individual nasal symptoms of the TNSS rated by the subjects during allergen challenge in the ECC on Day 1 and Day 8 of each treatment period, and gives the results of the comparison (p-values) between the two tested doses of BNO1355 (100 mg and 200 mg) and placebo.

Table 1: Allergic symptoms summarized as TNSS – Overview of results for Day 1 and Day 8

Allergic symtoms summarised as TNSS	Day 1			Day 8		
	BNO 1355 100 mg N=46 [points]	BNO 1355 200 mg N=47 [points]	Placebo N=47 [points]	BNO 1355 100 mg N=42 [points]	BNO 1355 200 mg N=42 [points]	Placebo N=44 [points]
Nasal congestion(0-4h)						
Mean	1.38	1.31	1.37	1.30	1.31	1.37
SD	0.43	0.63	0.59	0.51	0.58	0.53
200 mg vs Placebo		p=0.6040			p=0.4473	
100 mg vs Placebo		p=0.7505			p=0.7351	
Rhinorrhea(0-4h)						
Mean	1.27	1.28	1.29	1.28	1.36	1.35
SD	0.51	0.56	0.54	0.59	0.61	0.58
200 mg vs Placebo		p=0.9298			p=0.8382	
100 mg vs Placebo		p=0.9693			p=0.6186	
Nasal itching(0-4h)						
Mean	1.05	1.08	1.16	1.03	1.09	1.10
SD	0.52	0.59	0.56	0.46	0.53	0.48
200 mg vs Placebo		p=0.3357			p=0.7105	
100 mg vs Placebo		p=0.2437			p=0.7403	
Sneezing(0-4h)						
Mean	0.79	0.75	0.84	0.85	0.88	0.84
SD	0.37	0.40	0.33	0.37	0.37	0.38
200 mg vs Placebo		p=0.1821			p=0.1721	
100 mg vs Placebo		p=0.5730			p=0.3766	

Tables 2-4 show the mean values and SD for the evaluated primary and secondary efficacy endpoints and gives the results of the comparison (p-values) between the two tested doses of BNO1355 (100 mg and 200 mg) and placebo.

Name of Sponsor/Company: Bionorica SE	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: -	Volume:	
Name of Active Ingredient: Galphimia glauca dry extract BNO 1355	Page:	

Table 2: TNSS – Overview of results for Day 1 and Day 8

Total Nasal Symptom Score (TNSS)	Day 1			Day 8		
	BNO 1355 100 mg N=46 [points]	BNO 1355 200 mg N=47 [points]	Placebo N=47 [points]	BNO 1355 100 mg N=42 [points]	BNO 1355 200 mg N=42 [points]	Placebo N=44 [points]
$TNSS_{(2\text{-}4h)}$ = Primary endpoint						
Mean	5.03	4.95	5.16	4.99	5.31	5.23
SD	1.63	1.99	1.78	1.84	2.10	1.86
200 mg vs Placebo		p=0.5482			p=0.5541	
100 mg vs Placebo		p=0.8245			p=0.7376	
$TNSS_{(0\text{-}2h)}$ = Secondary endpoint						
Mean	3.96	3.88	4.15	3.94	3.97	4.06
SD	1.46	1.80	1.73	1.31	1.59	1.46
200 mg vs Placebo		p=0.3888			p=0.8334	
100 mg vs Placebo		p=0.6214			p=0.9410	
$TNSS_{max(0\text{-}4h)}$ = Secondary endpoint						
Mean	6.37	6.19	6.49	6.05	6.57	6.48
SD	1.68	2.16	2.06	1.94	2.20	1.98
200 mg vs Placebo		p=0.4162			p=0.6002	
100 mg vs Placebo		p=0.8373			p=0.3450	

Table 3: Nasal Flow rate – Overview of results for Day 1 and Day 8

Secondary endpoints	Day 1			Day 8		
	BNO 1355 100 mg N=46 [L/min]	BNO 1355 200 mg N=47 [L/min]	Placebo N=47 [L/min]	BNO 1355 100 mg N=42 [L/min]	BNO 1355 200 mg N=42 [L/min]	Placebo N=44 [L/min]
Nasal flow $rate_{(0\text{-}4h)}$						
• Relative change from baseline						
T1:30[1)]						
Mean	-0.434	-0.400	-0.449	-0.425	-0.444	-0.404
SD	0.336	0.335	0.360	0.353	0.335	0.309
200 mg vs Placebo		p=0.3549			p=0.4910	
100 mg vs Placebo		p=0.8171			p=0.4888	
T2:30[1)]						
Mean	-0.493	-0.476	-0.555	-0.500	-0.448	-0.525
SD	0.348	0.385	0.378	0.376	0.329	0.380
200 mg vs Placebo		p=0.1764			p=0.1630	
100 mg vs Placebo		p=0.2336			p=0.8548	
• Maximum decrease						
Mean	-319.5	-303.9	-324.8	-335.2	-322.7	-315.3
SD	188.7	183.7	179.4	217.6	196.5	184.6
200 mg vs Placebo		p=0.4065			p=0.7758	
100 mg vs Placebo		p=0.6935			p=0.5166	

1) Measurements 90 minutes (T1:30) and 150 minutes (T2:30) after start of allergen challenge.

Name of Sponsor/Company: Bionorica SE	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: -	Volume:	
Name of Active Ingredient: Galphimia glauca dry extract BNO 1355	Page:	

Table 4: Nasal secretion and sneezing – Overview of results for Day 1 and Day 8

Secondary endpoints	Day 1			Day 8		
	BNO 1355 100 mg N=46	BNO 1355 200 mg N=47	Placebo N=47	BNO 1355 100 mg N=42	BNO 1355 200 mg N=42	Placebo N=44
Nasal secretion (0-4h)	[gram]	[gram]	[gram]	[gram]	[gram]	[gram]
Mean	20.95	21.05	22.08	22.72	24.92	24.73
SD	12.46	14.30	14.28	15.07	14.90	13.96
200 mg vs Placebo		p=0.6001			p=0.7920	
100 mg vs Placebo		p=0.8611			p=0.2618	
Sneezing (0-4h)	[number of sneezes]	[number of sneezes]	[number of sneezes]	[number of sneezes]	[number of sneezes]	[number of sneezes]
Mean	25.17	28.43	27.45	30.60	31.05	29.20
SD	19.75	25.47	20.09	26.17	22.84	18.85
200 mg vs Placebo		p=0.6333			p=0.1941	
100 mg vs Placebo		p=0.8230			p=0.1898	

- Acute treatment effect (results of Day 1)

The differences between BNO 1355 (100 mg and 200 mg) and placebo in the mean values of subject-evaluated total nasal symptom scores averaged for the second half of a 4-hour allergen challenge with Dactylis glomerata pollen in the ECC ($TNSS_{(2-4h)}$ - first primary efficacy endpoint) were to small to reach statistical significance ($p>0.05$) on Day 1 (evaluation after first dose administration). During this interval, the mean $TNSS_{(2-4h)}$ values were smaller with 5.03 points for 100 mg BNO 1355 and 4.95 points for 200 mg BNO 1355 treatment compared to 5.16 points for placebo (see Table 2).The respective p-values of the pairwise tests were p=0.5482 (200 mg BNO 1355 vs placebo) and p=0.8245 (100 mg BNO 1355 vs placebo).

The period specific evaluation revealed a distinct decrease in the mean $TNSS_{(2-4h)}$ from Period 1 to Period 3 for 100 mg BNO 1355 (5.84 points vs 4.42 points), 200 mg BNO 1355 (5.65 points vs 4.01 points) and also for placebo (5.53 points vs 3.92 points) indicating an interaction between the $TNSS_{(2-4h)}$ and the period of assessment (significant period effect with $p<0.0001$ in the ANOVA). The result supports the conclusion that the severity of nasal symptoms during allergen challenge in this cross-over design was subject to influences that tend to decrease from period to period.

To avoid any bias on the treatment effect caused by subjects with incomplete treatment sequences, the analysis was repeated for the subgroup of subjects with complete treatment sequences (40 subjects). For this subgroup, the result were more pronounced in favour of the 200 mg BNO 1355 group vs placebo (p=0.2043) compared to the FAS population (p=0.5482) or PP set (p=0.3460). Similarily, no statistically significant differences were found on Day 1 ($p>0.05$) when comparing BNO 1355 (100 mg and 200 mg) and placebo regarding the expression of other key allergy targets in the nose ($TNSS_{(0-2h)}$, individual nasal symptoms of TNSS, including nasal congestion, rhinorrhea, nasal itching, and sneezing, as well as nasal flow rate, nasal secretion, and sneezing - secondary efficacy endpoints), as shown in Tables 1-4.

Name of Sponsor/Company: Bionorica SE	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: -	Volume:	
Name of Active Ingredient: Galphimia glauca dry extract BNO 1355	Page:	

- Prophylactic treatment effect (results of Day 8)

On Day 8, after 6 days of a three-times-a day dosing regimen (i.e., 300 mg BNO 1355/day, 600 mg BNO 1355/day, and placebo), no statistically significant differences were found when comparing the two dosages of BNO 1355 (100 mg and 200 mg) and placebo regarding the individual nasal symptoms of TNSS, and the primary and secondary endpoints, as shown in Tables 1-4). Similarly to Day 1, the period specific evaluation revealed a distinct decrease in the mean $TNSS_{(2\text{-}4h)}$ from Period 1 to Period 3 for both dosages of BNO 1355 (100 mg and 200 mg) and placebo.

Summary – Conclusions: Safety results

Sequential oral treatment with 100 mg and 200 mg BNO 1355 for 8 days each with maximum daily doses of 300 mg and 600 mg, respectively, was safe, well tolerated and, regarding the kind of AEs, comparable to placebo treatment.

- Adverse events

Throughout the whole study (Visit 3 to Visit 9), 79 AEs occurred in the 54 treated subjects (overall SEP). Thirty-five (35) of these 79 AEs started during or after treatment with 100 mg BNO 1355, 25 AEs with 200mg and 19 AEs with placebo. Overall, the most commonly reported AE was headache (26 out of 79 AEs, 32.9%) with a comparable incidence of occurrence during or after treatment with 100 mg BNO 1355 (34.3% of 35 AEs), 200 mg BNO 1355 (32.0% of 25 AEs) and placebo (31.6% of 19 AEs).

AEs were generally mild to moderate in intensity, and started more frequently during the 8-day treatment period than during the wash-out or follow-up periods. Seven (8.9%) out of 79 AEs were severe, 5 AEs occurring during treatment with 100 mg BNO1355 and 2 AEs during placebo treatment. Serious or fatal AEs were not reported.

According to the investigator's blinded assessment, 23 (29.1%) out of 79 AEs had a causal relationship to study treatment. Among these 23 adverse reactions (ARs), 12 ARs were considered related to 100 mg BNO 1355 (34.3% of 35 AEs), 5 ARs to 200 mg BNO 1355 (20.0% of 25 AEs) and 6 ARs to placebo (31.6% of 19 AEs). ARs most commonly affected the gastrointestinal tract (8 out of 12 ARs with 100 mg BNO 1355; 1 out of 5 ARs with 200 mg BNO 1355; 3 out of 6 ARs with placebo).

Overall, 13 AEs reported for 12 subjects resulted in permanent discontinuation of study medication. In 2 of these 12 subjects, the occurrence of an intolerable AE (eye infection and urinary tract infection) was the primary reason for premature discontinuation from study participation.

Change in concomitant medication was required less frequently for AEs reported during or after treatment with 100 mg and 200 mg BNO 1355 (34.3% of 35 AEs, and 32.0% of 25 AEs, respectively) than for AEs reported during or after treatment with placebo (42.1% of 19 AEs). All 79 AEs had resolved by the end of the study.

- Laboratory tests

All urine dipstick test results and haematological and biochemical laboratory values outside normal range were assessed as 'clinically not significant' except for a moderate transient change in liver enzymes (ALT, AST and LDH) in one subject detected only at the follow-up visit.

- Vital signs

There were not clinically relevant changes from baseline to follow-up in average blood pressure and pulse rate. The mean and maximum changes from Day 1 to Day 8 of each treatment period were small and clinically not relevant.

- Physical examination, ECG

The control physical examinations and control 12-lead ECG readings done did not reveal any clinically relevant changes compared to baseline.

- Lung function

Spirometry testing showed no clinically relevant changes in lung function from screening to follow-up measurements (maximum relative change of 6.6% in FEV1 and 9.2% in FVC). The maximum relative differences from Day 1 to Day 8 in pre-challenge FEV1 were comparable between 100 mg BNO 1355 and placebo (8.40% vs 8.30%) and less for 200 mg BNO 1355 (6.60%).

Name of Sponsor/Company: Bionorica SE	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: -	Volume: Page:	
Name of Active Ingredient: Galphimia glauca dry extract BNO 1355		

Treatment compliance

The average treatment compliance was nearly 100% with no relevant difference between 100 mg BNO 1355, 200 mg BNO 1355 and placebo (99.8±1.0%, 100.1±0.7% and 100.1±4.4%, respectively, according to pill count data in the CRF).

Conclusion

BNO 1355 (100 mg and 200 mg) failed to show an acute or prophylactic effect on nasal symptoms of seasonal allergic rhinitis triggered by allergen challenge with Dactylis glomerata pollen in a validated environmental challenge chamber. The observed period effect supports the conclusion that the severity of nasal symptoms during allergen challenge in this cross-over design was subject to influences that tend to decrease from period to period.
Treatment with BNO 1355 at daily doses up to 600 mg for a maximum of 8 days was safe and well tolerated and, regarding the kind of AEs, comparable to placebo treatment.

Date of the report: 15 DEC 2011 (Final Version)