Final Study report

Study title

Exploratory, disease activity controlled dose escalating study to assess the efficacy, and safety of treatment with bilastine 20 mg, 40 mg and 80 mg in chronic spontaneous urticaria

Short title: BUCSU
Treatment/Intervention: Bilastine
Eudra-CT Number: 2014-000181-21
Study Phase: III
Study duration: 02.07.2014 - 30.03.2016
ENR / ZNR Number: 2173799 - BE401387

Sponsor

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Version / Date - 1.0 / 22.02.2017

Study: BUCSU / Eudra-CT Number: 2014-000181-21

Name of Sponsor/Company:

Charité - Universitätsmedizin Berlin,
Allergie-Centrum-Charité

Name of Finished Product:

Bilastine (ATC-Code: R06AX29)

Name of Active Substance:

Bilastine (ATC-Code: R06AX29)

Product Code:

F-96221-BM1

Title of Study:

Exploratory, disease activity controlled dose escalating study to assess the efficacy, and safety of treatment with bilastine 20 mg, 40 mg and 80 mg
in chronic spontaneous urticaria.

Phase of development:

Study Phase: III (Bilastine 20mg daily is licensed, but not the updosing to 80mg)

Individual Study Table (Study Design):

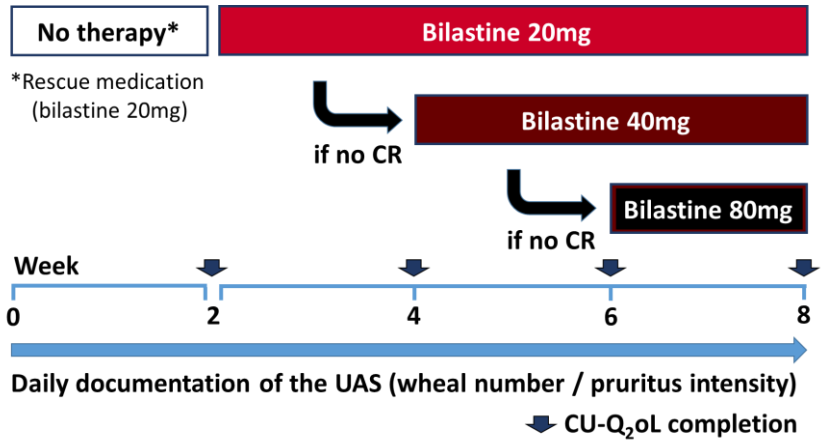

Figure 1 – Study design (CR – Complete response)

Principal Investigator:

PD Dr. med. Karsten Weller

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Publication:

It is intended to publish the results of this study irrespective of the results. The principal investigator is authorized to publish any data arising from the study, if the following conditions are considered: The work should be provided to the sponsor and to FAES FARMA for their information and comments. The sponsor, the principal investigator and FAES FARMA should agree on the content of the publication in advance. However, FAES FARMA would have the right to refuse only on scientific grounds.

Study period: 18 months

first patient in: 13.10.2014

last patient out (date of last completed): 05.03.2016

Objectives:

Primary:

- To assess the effects of standard dose (20 mg) and higher than standard dose of bilastine (40 mg and 80 mg) on disease activity in patients with chronic spontaneous urticaria.

Secondary:

- To assess the effects of standard dose (20 mg) and higher than standard dose of bilastine (40 mg and 80 mg) on quality of life impairment in patients with chronic spontaneous urticaria.
- To assess the safety of bilastine in doses of 20 mg, 40 mg and 80 mg in chronic spontaneous urticaria patients by documentation of adverse events.
- To assess the effects of standard dose (20 mg) and higher than standard dose of bilastine (40 mg and 80 mg) on biomarkers of chronic spontaneous urticaria, such as substance P and D-Dimers

Endpoints:

Primary:

- Comparison of the rate of complete responders (reduction of the UAS7 by at least 90% (as compared to baseline) or a UAS7 ≤ 3) between the second (20 mg bilastine), fourth (20 mg or 40 mg bilastine) and sixth week (20 mg, 40 mg or 80 mg bilastine) of the treatment phase.

Secondary:

- Comparison of additional responder rates between the second (20 mg bilastine), fourth (20 mg or 40 mg bilastine) and sixth week (20 mg, 40 mg or 80 mg bilastine) of the treatment phase.
- Comparison of the quality of life changes (based on the CU-Q_2oL) between baseline, the first/second (20 mg bilastine), third/fourth (20 mg or 40 mg bilastine) and fifth/sixth week (20 mg, 40 mg or 80 mg bilastine) of the treatment phase.
- Comparison of biomarker levels during no treatment and treatment with bilastine 20 mg, 40 mg and 80 mg.

- Description and comparison of the type and frequency of adverse events during treatment with bilastine 20 mg, 40 mg and 80 mg.

Methodology:

For the primary endpoint the rates of the (cumulative) complete responders between the different treatment periods were compared by using the exact McNemar test. For more details see protocol.

Relevant definitions of readouts:

- Complete response - Reduction of the UAS7 by at least 90% (as compared to baseline) or a UAS7 ≤ 3)
- Minimum urticaria activity: UAS7 ≤6
- Complete pruritus response: Reduction of the UAS7 pruritus score by at least 90% or Pruritus7≤1
- Minimum pruritus activity: UAS7 pruritus score ≤3

Number of patients (planned and analyzed)

A total number of 30 patients with moderate to severe chronic spontaneous urticaria, all of which had previously failed treatment with an antihistamine other than bilastine in standard (licensed) dose, were planned to be included into the study. Until the end of the trial, 31 patients were randomized and analyzed.

Diagnosis and main criteria for inclusion:

Diagnosis:

Chronic spontaneous urticaria

Main criteria for inclusion:

• Male or female aged 18 years and older
• History of active chronic spontaneous urticaria with or without associated angioedema for at least three days per week over the last 6 weeks prior to visit 1. Urticaria symptoms must comprise wheals and itch
• History of failed treatment with an antihistamine other than bilastine in standard (licensed) dose
• UAS7 of ≥14 during baseline
• Informed consent signed and dated
• Able to read, understand and willing to sign the informed consent form and abide with study procedures
• Willing, committed and able to return for all clinic visits and complete all study-related procedures
• In females of childbearing potential: negative pregnancy test; females willing to use highly effective contraception (Pearl-Index < 1). A woman was considered not of childbearing potential if she is post-menopausal for > 2 years or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy)
• No participation in other clinical trials 4 weeks before and after participation in this study

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Main criteria for exclusion:

• Chronic spontaneous urticaria patients with a known resistance to bilastine
• Isolated presence or domination of inducible forms of urticaria or cholinergic urticaria (no chronic spontaneous urticaria)
• History of adverse reactions to bilastine or known hypersensitivity to bilastine or its ingredients
• Intake of oral corticosteroids or intravenously applied corticosteroids within 28 days prior to screening visit
• Use of depot corticosteroids within 3 months prior to screening visit (inhaled corticosteroids are allowed)
• Use of systemic immunosupressants/immunomodulators such as ciclosporin, dapsone, metotrexate, and comparable drugs within 28 days prior to screening visit.
• Use of UV-therapy within 28 days prior to visit 1
• Significant medical condition, in the opinion of the Investigator, rendering the patient immunocompromised or not suitable for a clinical trial
• Significant concomitant illness, in the opinion of the Investigator, that would adversely affect the subject's participation or evaluation in this study
• ECG alterations of repolarisation (QTc prolongations >450ms or increase of QTc >60ms as compared to the baseline assessment)
• Blood pressure >180/100 mmHg and/or heart rate >100/min
• Evidence of significant hepatic or renal disease (GOT and/or GPT >2 times above the upper reference value, serum creatinine 1.5 times above the upper reference value)
• Subjects for whom there is concern, in the opinion of the Investigator, about compliance with the protocol procedures
• The presence of a permanent gastrointestinal condition which may influence the oral therapy (chronic diarrhoea diseases, congenital malformations or surgical mutilations of gastrointestinal tract)
• Presence of active cancer which requires chemotherapy or radiation therapy
• Presence of alcohol abuse or drug addiction
• Pregnancy or breast-feeding
• Subjects who are inmates of psychiatric wards, prisons, or other state institutions. Existing or planned placement in an institution after ruling according to § 40 passage 1, number 4 AMG (Arzneimittelgesetz).

Test product, dose and mode of administration, batch number

• Test product: Bilastine - 20 mg per tablet
• Dose: 20, 40 and 80 mg bilastine
• Mode of administration: Oral administration
• Batch-Number: 9349

Duration of treatment:

During the first two weeks (14 ± 2 days) of the study (screening phase) all patients were administered with one tablet bilastine 20 mg daily p.o. as rescue medication. This tablet

should only be taken in case of intolerable CSU symptoms and the intake had to be documented in the patient diary.
During the first two weeks (14 ± 2 days) of the following treatment phase all patients were asked to take one tablet bilastine 20 mg p.o. once daily. In case the patients did not achieve complete response (please see definition in section 18 Definitions), they changed to 40 mg bilastine p.o. (2 tablets containing bilastine 20 mg once daily) for the next two weeks (14 ± 2 days), while those with complete response stayed on 20 mg bilastine p.o. once daily for the rest of the study. After another two weeks, response to treatment was again reviewed. Those patients who did not achieve complete response to 40 mg bilastine p.o. were further updosed to 80 mg bilastine p.o. (4 tablets containing bilastine 20 mg once daily), while those with complete response stayed on the 40 mg dose p.o. for the rest of the trial. The total duration of the treatment phase was 6 weeks.

Reference therapy, dose and mode of administration, batch number

Not applicable

Criteria for evaluation:

The evaluation of efficacy and safety was carried out on the intention-to-treat population.

Main Efficacy, Safety Analyses:

• Responder rates (based on the UAS7 changes from baseline) during the second, fourth and sixth week of the treatment phase.

• CU-Q2oL values (change from baseline) during the first/second, third/fourth and fifth/sixth week of the treatment phase.

• Type and frequency of adverse events

Statistical methods:

For the primary endpoint (the rates of the (cumulative) complete responders between the different treatment periods) were compared by using the exact McNemar test: *p<0.05, **p<0.01, ***p<0.005, n.s. = not signicficant (p>0.05).
For secondary endpoints comparisons were performed by using the the exact McNemar test, the Wilcoxon Matched Pairs Signed Rank Test: *p<0.05, **p<0.01, ***p<0.005, n.s. = not signicficant (p>0.05). For correlations, the Pearson correlation coefficient was computed (according to Cohens conventions[1], a correlation coefficient of 0.1 to 0.3 was considered as weak correlation, 0.3 to 0.5 as moderate correlation, and >0.5 as large correlation). *p<0.05, **p<0.01, ***p<0.005, n.s. = not signicficant (p>0.05).
Missing items (in case of drop outs) were imputed by the LOCF (Last Observation Carried Forward) method. Missing items for D-Dimer and Vitamin D values were not replaced.

[1]Cohen J. Statistical power analysis for the behavioral sciences (2nd ed.). Hillsdale, NJ: Erlbaum, 1988.

RESULTS

Patient population:

Patients with a 7-day Urticaria Activity Score (UAS7) ≥14 at baseline (morderate to severe chronic spontaneous urticaria) who had previously failed treatment with a sgAH other than bilastine in licensed dose were eligible. In total, 31 patients were randomized. The patient characteristics are depicted in **Table 1**.

Number of patients	31
Gender ratio	24 females : 7 males
CSU duration (months) ± SD	58.7 ± 94.1
UAS7 ± SD	24.7 ± 8.0

Table 1 – Patient baseline characteristics

Primary endpoint:

The primary endpoint of this study was the comparison of the rate of complete responders (reduction of the UAS7 by at least 90% (as compared to baseline) or a UAS7 ≤ 3) between the first (20 mg bilastine), second (20 mg or 40 mg bilastine) and third (20 mg, 40 mg or 80 mg bilastine) treatment phase. The results on the primary endpoint are shown in **Table 2**.

Study phase	n of patients	Complete responder (cumulative)	Non-complete responder	McNemar-Test[1] Exact Sig. (1-tailed)
Baseline	31	0	31	--
Bilastine 20mg	31	6	25	0.016
Bilastine 40 mg	30	9	21	0.125
Bilastine 80 mg	29	9	20	1.000

Table 2 – Complete responders in different study phases (primary endpoint)
[1]McNemar-test test the increase of complete responders with regard to the previous treatment phase

In total, 9 patients showed a CR during the study (UAS≤3); 6 patients to bilastine 20mg

and 3 patients to bilastine 40mg (**Figure 2A**). The comparison between the first (20 mg bilastine), second (20 mg or 40 mg bilastine) and third (20 mg, 40 mg or 80 mg bilastine) treatment phase was not statistically significant.

The comparison between the responder rates in the baseline phase and the first treatment phase (not primary endpoint) was statistically significant ($p<0.05$).

Secondary endpoints:

When applying a less strict criteria for response (minimal disease activity - UAS7≤6 instead of UAS≤3), eleven patients achieved minimal urticaria activity, 8 on bilastine 20mg, 2 patients on bilastine 40mg, and 1 patient on bilastine 80mg (**Table 3**, **Figure 2A**). The comparison between the first (20 mg bilastine) and second (20 mg or 40 mg bilastine) was statistically significant.

Study phase	**n of patients**	**Patients achieving minimal disease activity (UAS7≤6)**	**Patients not achieving minimal disease activity (UAS7>6)**	**McNemar-Test[1] Exact Sig. (1-tailed)**
Baseline	31	0	31	--
Bilastine 20mg	31	8	23	0,004
Bilastine 40 mg	30	10	19	0,250
Bilastine 80 mg	29	11	16	0,500

Table 2 – Patients achieving minimal disease activity in different study phases (primary endpoint)
[1]McNemar-test test the increase of Patients achieving minimal disease activity with regard to the previous treatment phase

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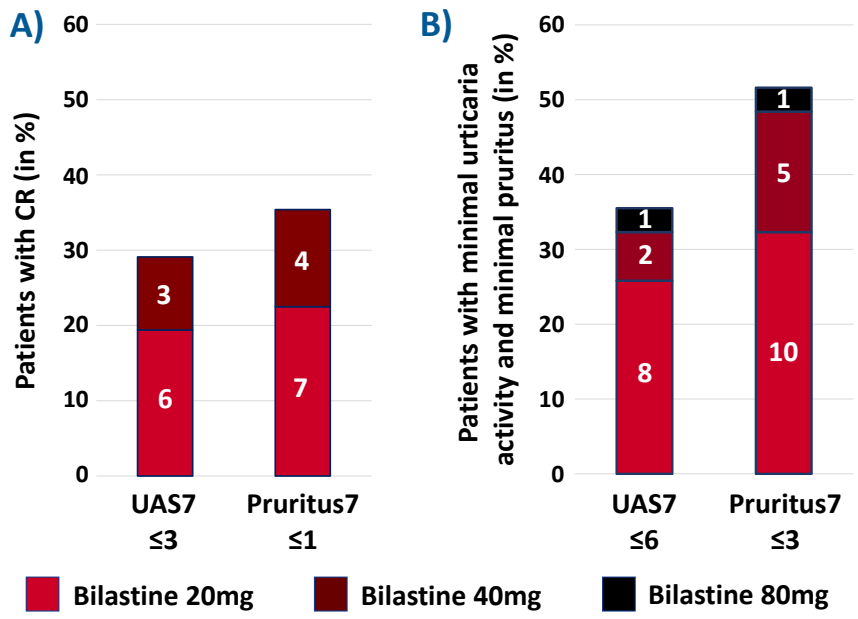

Figure 2 – Response rates to bilastine 20mg, 40 mg, and 80 mg

Focusing on the pruritus component, 7 patients showed a CR (Pruritus7≤1) to bilastine 20mg, and 4 patients to bilastine 40mg. Sixteen patients achieved a minimal pruritus (Pruritus7≤3), 10 on bilastine 20mg, 5 on bilastine 40mg, and 1 on bilastine 80mg (**Figure 2B**).

The mean UAS7 and Pruritus7, respectively, decreased significantly to 15.3±10.8 and 7.0±5.3 during bilastine 20mg (both p<0.005) as compared to baseline (24.7±8.0 and 12.7±4.1). The reductions are shown in **Figure 3** and **Figure 4**.

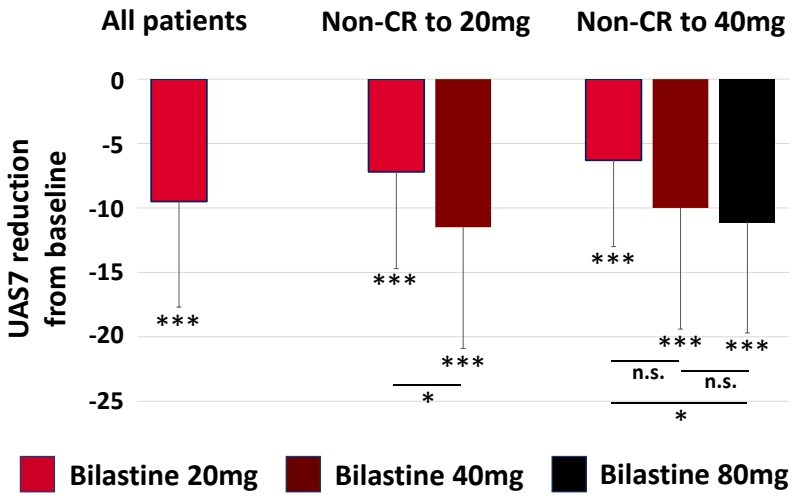

Figure 3 – Urticaria activity decreases during bilastine treatment and updosing

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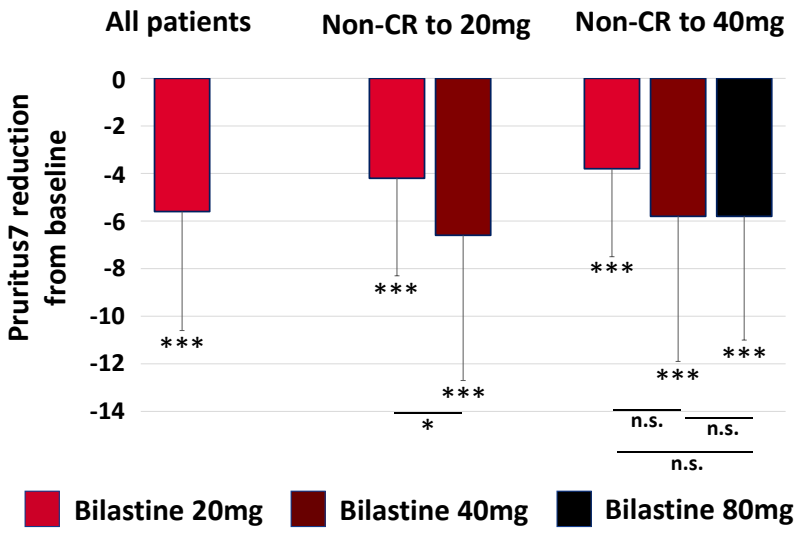

Figure 4 – Pruritus decreases during bilastine treatment and updosing

In those patients not completely responding to 20mg, the mean UAS7 and mean Pruritus7 significantly decreased from 18.7±9.1 and 8.6±4.7 during 20mg treatment to 14.4±7.5 and 6.3±4.9 during 40mg treatment (both $p<0.05$). In patients also not completely responding to 40mg, the mean UAS7 but not the Pruritus7 showed a further albeit not significant decrease during 80mg treatment, but individual patients profited differently well. The decrease of the mean UAS7 and Pruritus7 from baseline (26.4±8.6 and 12.9±4.4) to 80mg treatment (15.3±6.3 and 7.1±4.8) was significant also in this group (both $p<0.005$).

The mean CU-Q_2oL total score decreased significantly to 19.9±10.2 during bilastine 20mg ($p<0.005$) as compared to baseline (27.4±11.8). The reductions are shown in **Figure 5**. In those patients not completely responding to 20mg, the CU-Q_2oL total score significantly decreased from 22.8±8.7 during 20mg treatment to 19.8±11.3 during 40mg treatment ($p<0.05$). In patients also not completely responding to 40mg, the mean CU-Q_2oL total score did not further decrease during 80mg treatment, but instead showed a non-significant increase from 21.3±10.9 to 23.5±11.9. The decrease of the mean CU-Q2oL total score from baseline (29.0±11.3) to 80mg treatment (23.5±11.9) was significant also in this group (both $p<0.05$).

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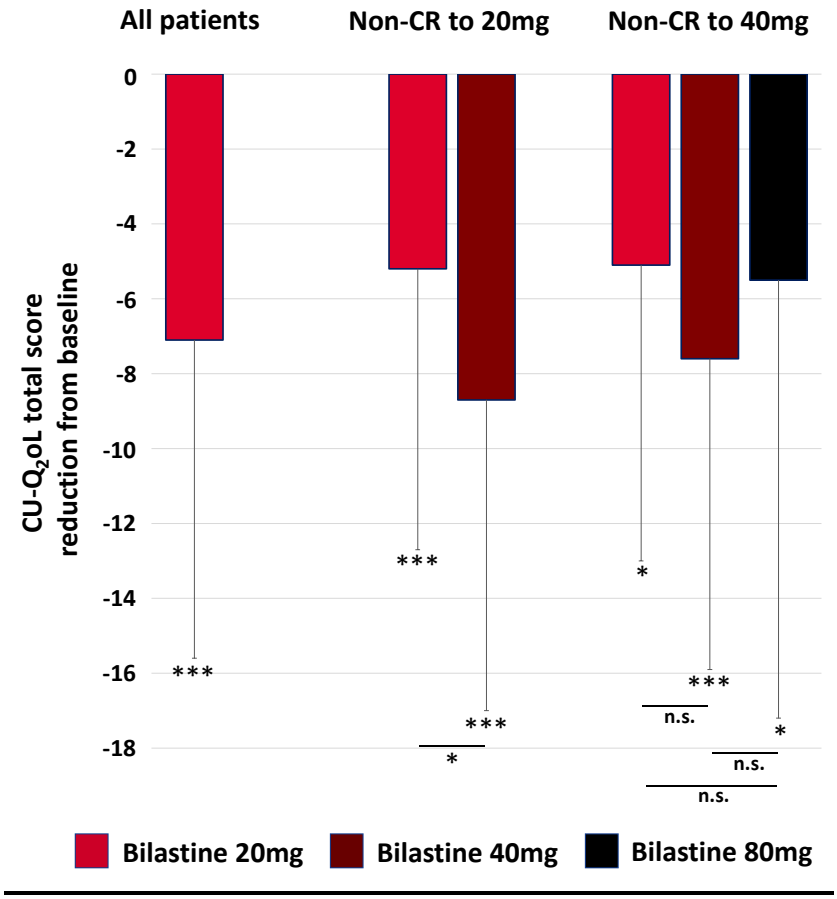

Figure 5 – Urticaria-related quality of life impairment improves during bilastine treatment and updosing

The mean D-Dimer (in mg/l, reference value <0.5) and Vitamin D (25-OH-Vitamin D in nmol/l, reference range 50-150) levels, respectively, were 0.82±0.62 and 49.3±23.9 at baseline and changed to 0.62±0.41 and 50.4±20.3 during bilastine 20mg (both not significant). The changes are shown in **Figure 6** and **Figure 7**.

In those patients not completely responding to 20mg, the mean D-Dimer and Vitamin D levels changed from 0.65±0.44 and 49.9±20.1 during 20mg treatment to 0.63±0.42 and 53.6±21.6 during 40mg treatment (both not significant). In patients also not completely responding to 40mg, the mean D-Dimer and Vitamin D levels showed a change from 0.65±0.43 and 54.8±22.3 during 40mg treatment to 0.75±0.58 and 54.4±27.5 during 80mg treatment (both not significant).

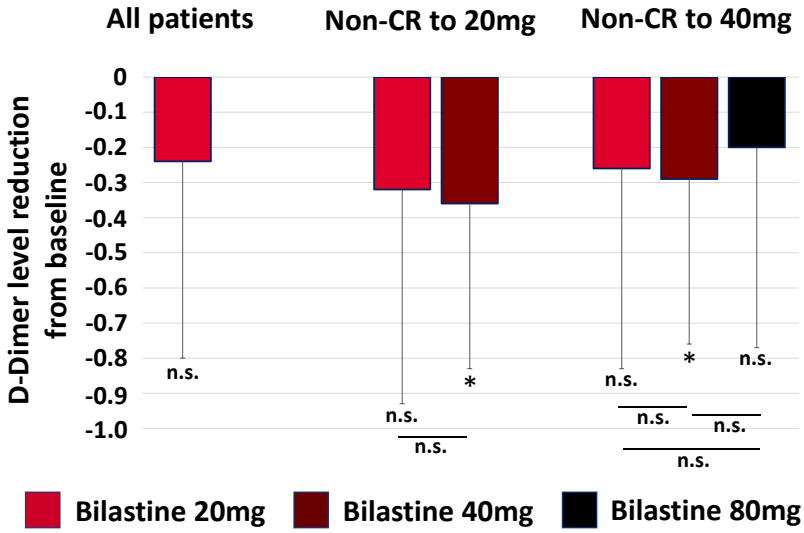

Figure 6 – D-Dimer level changes during bilastine treatment and updosing

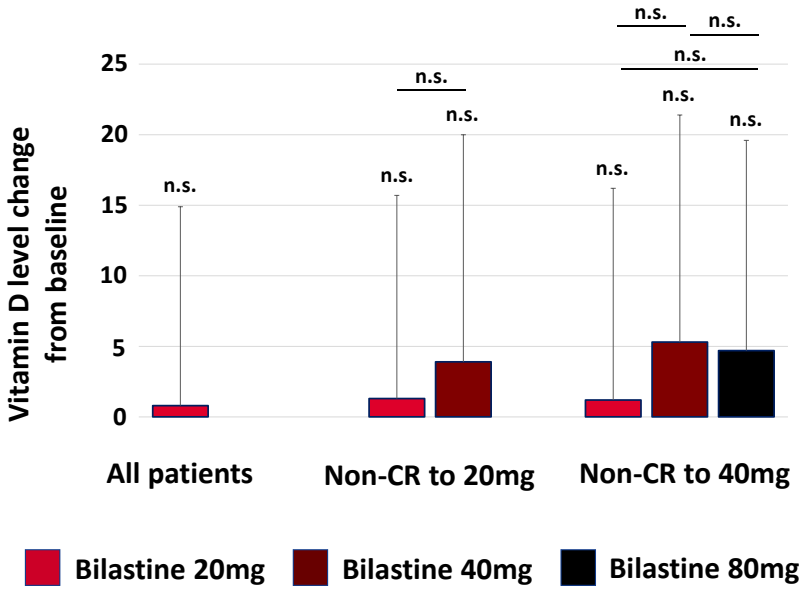

Figure 7 – Vitamin D level changes during bilastine treatment and updosing

D-Dimer levels and Vitamin-D levels were applied as possible biomarkers for disease activity. However, there was no significant correlation ($p>0.05$) between UAS7 values at baseline and D-Dimer levels and Vitamin D levels at baseline (correlation coefficients: $r=0.27$ and $r=0.09$, respectively). In addition, there was also no significant correlation ($p>0.05$) between the UAS7 change from baseline to 20 mg treatment with the D-Dimer level changes and the Vitamin D level changes (correlation coefficients: $r=0.10$ and $r=0.08$, respectively). This correlation analysis suggests that both, D-Dimers and Vitamin D, are no reliable biomarkers for disease activity and changes of disease activity over time in chronic spontaneous urticaria, which is in accordance with other recent works[2].

[2]Weller et al. D-Dimers are not a reliable biomarker for disease activity in chronic spontaneous urticaria patients. Exp Dermatol 2016; 25, E2 P009

Safety:

No relevant differences occurred with regard to the frequency of adverse events between the four study phases. An overview of the frequency of adverse events is shown in Table 3.

	Baseline (n=31)	**Bilastine 20 mg (n=31)**	**Bilastine 40 mg (n=31)**	**Bilastine 80 mg (n=27)**
Total number of adverse events	15	19	13	6
Total number of serious adverse events	1*	0	0	0
Patients with any adverse event	11	15	7	6
Patients with any serious adverse event	1*			
Discontinuation due to adverse event			2	

Table 3 – Overview on adverse events during the course of the study.
*Hypertensive Crisis with exsiccosis and dyspepsia which required hospitalization. Relation to study medication was rated unlikely (occurrence in baseline phase). The patient completely recovered and continued to take part in the study.

The complete list of adverse events is provided in **Table 4**.

	Baseline (n=31)	**Bilastine 20 mg (n=31)**	**Bilastine 40 mg (n=31)**	**Bilastine 80 mg (n=27)**
Neurological				
Headache (R51)	8	5	2	3
Tiredness (R53)		6	1	1
Migrane (G43.9)		1		
Dizziness (R42)			1	
Hepato-Gastrointestinal				
Stomach cramps (R10.4)	1			
Stomachache (R10.4)		1	2	
Constipation (K59.0)	1			1
Diarrhea (A09.9)			2	
Nausea (R11)			1	
Respiratory				
Infection of the upper airways (J06.9)	2	1	4	1
Genito-Urinary				
Asymptomatic urinary tract infection (N39.0)	1			
Dysmenorrhea (N94.6)	1			
Cardiovascular				
Hypertension (I10.9)	1	1		
Skin				
Alopecia areata (L63.9)		1		

Flaking of the scalp (n/a)		1		
Musculoskeletal				
Elevation of lab value creatinkinase (n/a)		1		
Ear-Nose-Throat				
Itch of the palate/Urge to sneeze (L29.9)				
Other				
Chills (n/a)		1		

Table 4 – Complete list of adverse events that occurred during the course of the study.

The only serious adverse event of this study occurred during the baseline phase (hypertensive crisis with exsiccosis and dyspepsia which required hospitalization). Relation to study medication was rated unlikely (occurrence in baseline phase). The patient completely recovered and continued to take part in the study.

The most common adverse events during the study were tiredness and headache. Notably, the frequency of these adverse events did not increase with increasing doses of bilastine.

Conclusions:

- Bilastine is effective in moderate to severe CSU patients not responding sufficiently to other sgAHs in licensed dose.
- Some patients completely respond to 20mg bilastine, others require an updosing to 40mg or 80mg to achieve a marked symptom reduction. (However, Bilastine failed to significantly increase the rate of complete responders during updosing in this study).
- Bilastine significantly reduces signs and symptoms of CSU (UAS7 and Pruritus7 scores) but also urticaria-related health-related quality of life impairment (CU-Q_2oL total score)
- Bilastine is safe in licensed (20mg) and up to four times the licensed dose (40mg und 80 mg). Notably, adverse events, particularly the most common events headache and tiredness, did not increase with bilastine updosing. No treatment-related SAE occurred in the study.
- D-Dimers and Vitamin D levels are no reliable biomarkers of disease activity in CSU

Date of report:

February 22nd 2017