time-to-minimum symptoms (TTMS) and TOSR by self-assessed pain scale (Faces Pain Scale-Revised tool). Safety and effect on reproductive hormone levels were assessed.

Results: In part 1, 32 patients (aged 2 to <18 years) were treated. In part 2, 9 adolescent patients had >1 icatibant exposure; 5 were female, mean (SD) age at 2nd exposure in adolescent patients was 17.4 (2.45) years. Eight patients had cutaneous, abdominal or cutaneous/abdominal HAE attacks; 1 patient had 2 laryngeal HAE attacks in part 2. Median TOSR for 2nd (n = 9) and 3rd (n = 8) exposure was 1.0 h (95% CI 1.0-2.3) and 1.1 h (95% CI 1.0-3.0), respectively. Median TTMS was 1.2 h (95% CI 1.0-2.0; n = 7) and 2.2 h (95% CI 1.0 to not estimable; n = 7 [2 censored]), respectively. Median TOSR by self-assessed pain scale (n = 8) was 1.1 h (95% CI 1.0-2.1) and 1.0 h (95% CI 1.0-1.2), respectively. Treatment-emergent adverse events (TEAEs) occurred in 4 patients after 2nd exposure and 5 patients after 3rd exposure. All were mild/moderate except for 2 severe, non-drug-related TEAEs after 3rd exposure (folliculitis and ear pain). Infections and infestations (n = 3; 3 events) was the most common SOC. There were no serious TEAEs, discontinuations due to TEAEs, or clinically significant changes in reproductive hormone levels.

Conclusion: Given the recurring nature of HAE attacks, the sustained effect, rapid response and tolerability after repeated exposure indicate that icatibant is an important and safe treatment option for adolescent patients with C1-INH-HAE.

PD0377 | A missense mutation of the plasminogen gene in hereditary angioedema with normal C1 inhibitor in Japan

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Background: Hereditary angioedema with normal C1 inhibitor (HAEnCI) is a novel type of HAE whose genetic background is heterogeneous. Mutations in the factor XII (*F12*) gene have been reported almost exclusively from Caucasians, while none from other races including Asians. The genetic abnormalities causing HAEnCI in Asians were still unknown. Recently, a missense mutation K330E located in exon 9 of the plasminogen (*PLG*) gene was identified in German HAEnCI patients.

Method: We performed a genetic study to see the presence of K330E in the *PLG* gene in our 20 Japanese unrelated HAEnCI families.

Results: Four members (3 females, 1 male) from two families were carrying heterozygously K330E mutation. All of them experienced recurrent episodes of angioedema, especially in tongue and lip.

Conclusion: To our knowledge, this is the first report that clarified the genetic basis of HAEnCI in Asians.

PD0378 | Omalizumab treatment, re-treatment and step-up treatment associated with reduced angioedema rates: Results from the optima study

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Background: Chronic idiopathic urticaria (CIU)/chronic spontaneous urticaria (CSU) is primarily considered an autoimmune disease with intermittent symptoms characterized by the triad of itch, hives and angioedema, with 50% of patients suffering from all three. OPTIMA (NCT012161562) is a novel study gathering data on optimal treatment of CIU/CSU with omalizumab (OMA). Previous analyses focused on the impact of OMA on itch and hive scores. The current analysis focuses on its impact on angioedema, a critical CIU/CSU symptom associated with poor prognosis.

Method: OPTIMA is a Phase 3b, international, multicenter, randomized, open-label, noncomparator study. Patients with CIU/CSU and symptomatic despite H1-antagonists were initially randomized 4:3 to omalizumab 150 or 300 mg for 24 weeks (1st dosing period). Based on Urticaria Activity Score over 7 days (UAS7) scores, patients were then divided in groups: step-up (from 150 to 300 mg if UAS7 >6 between week 8-24); retreatment (if UAS7 ≤ 6 at week 24, withdrawal and re-treatment with same dosage if UAS7 ≥ 16 during withdrawal); or extension (if 300 mg initially and UAS7 >6 at week 24, continuing treatment for 12 weeks).

Results: A total of 314 patients (73% female, 79% white, mean age 46 years, mean baseline (BL) UAS7 score 29.8) were included into this analysis. 56.1% of patients suffered from angioedema at BL, and 61.5% had at least one angioedema episode during the 12 months prior to screening (38.3% ≥ once per week and 26.9% ≥ once per month). For all patients, regardless of their UAS7 response to OMA, the average weekly number of angioedema episodes (AWAE) declined from 2.15 at BL to 0.79 in the 1st dosing phase. When patients were categorized based on their UAS7 response to OMA, a similar response was seen between control achieved for angioedema and for itch and hives (previously reported). The 300 mg retreated patients had their AWAE reduced from 2.70 at BL to 0.22 during 1st dosing period (24 weeks), increased to 1.23 during withdrawal period (up to 8 weeks) and decreased to 0.29 during the 2nd dosing period (12 weeks). Furthermore, the step up patients had their

AWAE reduced from 1.21 during the 1st dosing period (150 mg), to 0.69 during 2nd dosing period (300 mg).

Conclusion: When patients are treated based on their UAS7 response to OMA, the treatment response for angioedema follows a similar pattern to that of the itch and hives throughout the different treatment phases, including reoccurrence upon withdrawal and responsiveness to re-treatment.

PD0379 | Role of vascular permeability factors in patients with normal C1-INH angioedema

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Background: Angioedema is identified by submucosal and subcutaneous edema of skin, larynx and abdomen due to increased vascular permeability. Different angioedema types were classified into hereditary and acquired angioedema. Hereditary angioedema (HAE) can be caused by deficiency of C1 esterase inhibitor (C1-INH-HAE), mutations in the gene for Factor XII (FXII-HAE), for plasminogen (PLG-HAE) and for angiopoietin 1 (ANGPT1-HAE). A large group of patients is still classified as angioedema of unknown origin (U-HAE). We previously reported that plasma levels of cleaved high molecular weight kininogen (cHK), vascular permeability factors such as Vascular Endothelial Growth Factors (VEGFs), Angiopoietins (Angs) and secreted phospholipase A_2 enzymes ($sPLA_2$) were increased in C1-INH-HAE patients compared to healthy controls. In order to identify specific biomarkers in different forms of HAE, we measured cHK (as indirect evidence of bradykinin generation), VEGFs and Angs concentrations and $sPLA_2$ activity in patients with FXII- and U-HAE.

Method: 15 FXII-HAE patients and 32 U-HAE patients vs 34 healthy controls were studied. Plasma concentrations of angiogenic (VEGF-A, Ang1, Ang2) and lymphangiogenic (VEGF-C) factors were evaluated by ELISA, cHK by Western Blot and $sPLA_2$ activity was evaluated by EIA.

Results: Firstly, we evaluated cHK levels using plasma sampling with sodium citrate or with a mixture of inhibitors. Interestingly, cHK levels in U-HAE patients were similar to controls when plasma was collected using protease inhibitors, but they were significantly increased when measured in sodium citrate sample. Then, we found a significant increase of VEGF-A, VEGF-C and Ang1 levels in U-HAE patients compared to controls. By contrast, in FXII-HAE only VEGF-C levels were significantly increased. Ang2 concentrations and $sPLA_2$ activity were not modified in both the HAE groups. Finally, we did not find any correlation among cHK and VEGFs and Angs.

Conclusion: Our results on different plasma sampling seem to confirm the bradykinin-mediated pathogenesis of FXII- and U-HAE. Similarly to C1-INH-HAE, VEGFs and Ang1 could play a crucial role in the pathophysiology of U-HAE increasing the basal vascular permeability of these patients.

Several studies and samples expansion are needed to better understand the molecular mechanism behind these angioedema types.

PD0380 | A new instrument for the evaluation of premonitory signs and symptoms (Prodromes) of hereditary angioedema

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Background: Attacks of Hereditary Angioedema (HAE) are considered unpredictable and variable in location and intensity. Many HAE patients describe premonitory signs and symptoms (Prodromes), which antedate and associated with the attacks. Albeit frequently reported, prodromes have not been adequately investigated, and systematic tools for their evaluation are lacking. A reliable prodrome evaluation tools can assist in timing of medical interventions, thereby help to shorten the painful, disabling and life-threatening attacks.

Method: From 233 Israeli HAE patients, 197 (84.5%) responded to a survey asking if they ever had a prodrome, and if they can predict an oncoming attack by having a prodrome. Mean age of the cohort was 36.7 ± 20.3 years (range: 2-80, females 42.5%). Mean age of onset of HAE attacks was 10.7 ± 10.3Y, while age of diagnosis was 15.5 ± 15.1Y. Nearly 62% of this group were diagnosed by age 10 (M>F, $P < 0.05$). Sixty six (33.5%) completed a questionnaire, developed specifically to evaluate experience with prodromes and attacks. It covers 6 "clusters" of body systems, often affected during both events. Primary aim was to analyze the incidence and association between prodromes and subsequent attacks. Secondary aim was to assess if patients could distinguish between the dimensions of prodromes from similar dimensions of attacks at the same locations.

Results: Main triggers of attacks were physical trauma (69%) and stress (46%). 165/197 (84%) reported ever having a prodrome. 143/165 (87%) could predict an oncoming attack by experiencing a prodrome. There was a significant correlation between prodromes and attacks ($P < 0.01$, $r = 0.79$), with no gender predominance ($t = 0.03$, $P > 0.05$). In order to check differences between clinical dimensions of prodromes and attacks, we performed one-way ANOVA with repeated measurements, on responses of patients who completed the new questionnaire (N = 66). Analysis shows that