Durability of Symptom Control with Long-term Prophylactic Therapy With Subcutaneous C1-Inhibitor in Patients With Hereditary Angioedema

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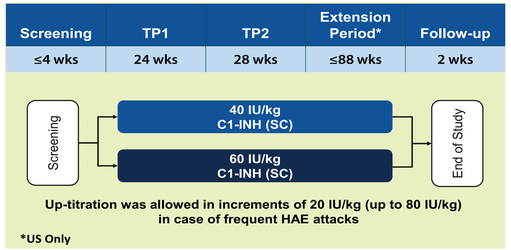
INTRODUCTION

- Hereditary angioedema (HAE) due to C1-inhibitor (C1-INH) deficiency is characterized by recurrent nonpruritic edema that commonly affects the face, limbs, and trunk, and submucosal tissues of the gastrointestinal, genitourinary, and upper respiratory tracts.[1,2] Attacks may be disfiguring, painful, and, in the case of upper airway involvement, potentially fatal.[3,4]
- Subcutaneous C1-inhibitor (C1-INH [SC] 60 IU/kg, HAEGARDA®, CSL Behring) is indicated for routine prophylaxis to prevent attacks in adolescent and adult patients with HAE.[5] Efficacy and safety of C1-INH (SC) was demonstrated in a placebo-controlled phase III trial (COMPACT) and an open-label extension (OLE) of this trial.[6,7] The primary objective of the OLE was to assess the long-term safety of C1-INH (SC).[7]
- Here, we present efficacy data and patterns of rescue medication use from the OLE, in which patients were treated with C1-INH (SC) 60 IU/kg for up to 140 weeks (~2.7 years).

METHODS

- The OLE of the COMPACT trial was a multicenter, randomized, parallel-arm study and included patients who had completed the placebo-controlled COMPACT trial, as well as C1-INH (SC)-naive patients. Eligible patients (age ≥6 years with ≥2 attacks per month before enrollment in the OLE or the COMPACT trial) were randomly assigned to receive C1-INH (SC) at 40 IU/kg or 60 IU/kg twice weekly for 52 weeks. Patients in the United States were eligible to continue treatment for up to 140 weeks (**Figure 1**).
- The efficacy endpoints included:
  - Percentage of patients with a time-normalized attack rate <1 attack per 4-week period
  - Percentage of responders (≥50% reduction in attacks vs pre-study)
  - Use of rescue medication

Figure 1. *COMPACT Open-label Extension Study Design*



RESULTS

- A total of 126 patients were randomized to treatment (40 IU/kg: n=63; 60 IU/kg: n=63). Data for the FDA-approved 60 IU/kg dose are presented.
- Before entry into either COMPACT or COMPACT OLE, the median pre-study 3-month attack rate was 9 in patients randomized to 60 IU/kg.

Impact of C1-INH (SC) 60 IU/kg on HAE attacks

- There were a total of 371 attacks reported in the 60 IU/kg treatment arm over an observation period of up to ~2.7 years.
- The median (range) attacks per month and year were 0.09 (0.0-4.0) and 1.0 (0.0-48.0), respectively.
- The percentage of responders, defined as ≥50% reduction in attacks vs pre-study, was 92.7% and 31 (49.2%) patients experienced <1 attack per year.
- In patients with more than 2 years exposure, 19 (82.6%) of 23 were completely attack-free in the observation period from months 25 to 30.

Impact of C1-INH (SC) 60 IU/kg on rescue medication use

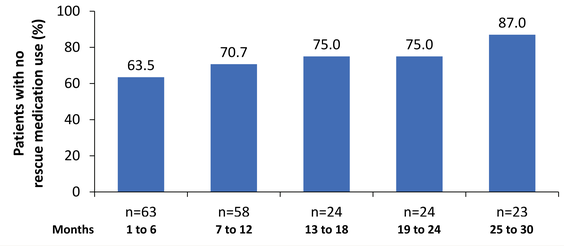
- Of the 371 HAE attacks that were reported during the entire duration of the OLE, 229 (61.7%) were treated with on-demand rescue medications. Of the 229 treated attacks, 83.8% (192/229) resolved with 1 dose of rescue medication (**Table 1**).
- Thirty-nine (61.9%) of patients on 60 IU/kg didn't use HAE on demand treatment while 24 (38.1%) had at least 1 attack requiring treatment during the OLE that lasted up to 140 weeks.
- The mean (SD) and median (range) numbers of treated HAE attacks per month were 0.27 (0.66) and 0.00 (0.00-3.87), respectively.

Table 1. *Patterns of Retreatment of Acute Attacks With C1-INH (SC) 60 IU/kg*

Uses of Rescue Medication, n	Patients With Treated Attacks (N=63), n (%)	Treated Attacks (N=229), n (%)
1	24 (38.1)	192 (83.8)
2	6 (9.5)	25 (10.9)
3	4 (6.3)	7 (3.1)
>3	1 (1.6)	5 (2.2)

- The majority of treated attacks were treated with plasma-derived C1-INH (IV) or icatibant. No attacks were treated with recombinant C1-INH or fresh frozen plasma.
- Of the 229 attacks that required treatment, 49% were severe, 39% were moderate, and 12% were mild. The mean (SD) severity of treated attacks was 1.97 (0.58) (1=mild, 2=moderate, 3=severe).
- Post-hoc analysis of annualized on-demand medication use showed that 39 patients (61.9%) treated with C1-INH (SC) 60 IU/kg used no on-demand medication; 66.7% used on-demand medication less than once per year (mean [SD]: 3.8 [9.6] uses/year; median: 0.0 uses/year).
- The use of on-demand medication remained consistently low and the percentage of patients requiring on-demand treatment decreased over time throughout the study period.
- Consistent with these results, median attack-free duration before first attack was 223 days. Eighty-three percent of patients (19/23) treated with C1-INH (SC) 60 IU/kg for more than 2 years were completely attack-free between months 25 and 30.

Figure 2. *Percentage of Patients With No Rescue Medication Use Treated With C1-INH (SC) 60 IU/kg for >2 Years**



* Only 5 patients had an exposure to C1-INH (SC) 60 IU/kg for more than 30 months.

- An analysis of the subgroup of patients treated for more than 2 years in the OLE trial showed that between months 25 and 30, 87% (20/23) used no on-demand medication. (**Figure 2**).

CONCLUSIONS

- Long-term use of C1-INH (SC) 60 IU/kg demonstrates sustained efficacy for up to 2.7 years.
- In this severely affected patient population, C1-INH (SC) 60 IU/kg was effective for the prophylactic treatment of HAE.
  - The median annualized attack rate was reduced to 1.0 attack per year.
  - Median attack-free duration until first attack was 223 days.
  - Rescue medication use was low with ~two-thirds of patients requiring no rescue medication use and a median annualized use of 0.0 per year.

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