The Icatibant Outcome Survey: 10 years of experience with icatibant for patients with hereditary angioedema

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Abstract
In patients with hereditary angioedema (HAE), bradykinin causes swelling episodes by activating bradykinin B2 receptors. Icatibant, a selective bradykinin B2 receptor antagonist, is approved for on-demand treatment of HAE attacks. The Icatibant Outcome Survey (IOS; NCT01034969) is an ongoing observational registry initiated in 2009 to monitor the effectiveness/safety of icatibant in routine clinical practice. As of March 2019, 549 patients with HAE type 1 or 2 from the IOS registry had been treated of 5995 total attacks. This article reviews data published from IOS over time which have demonstrated that the effectiveness of icatibant in a real-world setting is comparable to efficacy in clinical trials; one dose is effective for the majority of attacks; early treatment (facilitated by self-administration) leads to faster resolution and shorter attack duration; effectiveness/safety of icatibant has been shown across a broad range of patient subgroups, including children/adolescents and patients with HAE with normal C1 inhibitor levels; and tolerability has been demonstrated in patients aged ≥65 years. Additionally, this review highlights how IOS data have provided valuable insights into patients’ diagnostic journeys and treatment behaviours across individual countries. Such findings have helped to inform clinical strategies and guidelines to optimise HAE management and limit disease burden.
Hereditary angioedema (HAE) is a rare disease associated with recurrent attacks of subcutaneous/submucosal tissue swelling. Attacks are unpredictable in frequency, severity and location. The emotional burden and functional limitations can be substantial, leading to impairment in patients' quality of life and a substantial negative impact on families/caregivers.

Considerable progress has been made in understanding underlying pathophysiology and identifying HAE subtypes. The presence of mutations in the SERPING-1 gene results in deficiency and/or dysfunction of C1 inhibitor (C1-INH; HAE type 1 or 2 [HAE-1/2]). As shown in Figure S1, C1-INH, a serine protease, downregulates the activity of several key drivers of bradykinin generation by the contact system (kallikrein–kinin signalling cascade), including factor XIIa and plasma kallikrein. Bradykinin, a potent vasodilator, causes HAE-associated tissue swelling/oedema by acting on the bradykinin B2 receptor. In patients with HAE-1/2, insufficient levels or dysfunctional activity of C1-INH lead to uninhibited signalling within the kallikrein–kinin pathway, resulting in excessive bradykinin production.

Hereditary angioedema may also occur in patients with normal levels or function of C1-INH (HAE nC1-INH). Several genetic mutations have been reported (including angiopoietin-1, factor XII, kininogen-1, plasminogen and myoferlin), although the underlying cause is often unknown. Bradykinin may also play an important underlying role in HAE nC1-INH clinical manifestations.

Research strides have led to the development/approval of eight agents to date, targeting various aspects of the kallikrein–kinin pathway (approvals vary by country); sites of action of select agents are shown in Figure S1. Icatibant (Firazyr®, Takeda Pharmaceuticals USA, Inc.) is a potent and selective antagonist of the bradykinin B2 receptor.

Efficacy/safety of icatibant for acute attacks in patients with HAE-1/2 was demonstrated in three pivotal phase 3 randomised controlled trials with open-label extensions. Briefly,
in FAST-1/FAST-2, treatment of cutaneous or abdominal attacks with icatibant was compared with placebo or tranexamic acid respectively.12 The primary end-point, median time to clinically significant relief of the index symptom, was 2.5 vs. 4.6 h (p = .14) in FAST-1, and 2 vs. 12 h (p < .001) in FAST-2. Statistical significance for the primary end-point in FAST-1 was not met, possibly because only the index symptom was used to define symptom relief, and data from placebo patients with early use of rescue medications were included. In FAST-3, the primary end-point, median time to ≥50.0% reduction in symptom severity, was significantly shorter with icatibant vs. placebo: 2 vs. 19.8 h (p < .001) for cutaneous or abdominal attacks (at least moderate severity), and 2.5 vs. 3.2 h for mild-to-moderate laryngeal attacks (statistical comparison not conducted due to small patient numbers).13 There were no icatibant-related serious adverse events (SAEs) reported in any of the controlled studies, or within the FAST-1/FAST-2 open-label studies; however, in the FAST-3 open-label extension, two SAEs were considered related to icatibant (non-cardiac chest pain and arrhythmia).12-16

Following results from controlled trials, icatibant was approved in 2008 for treatment of acute HAE attacks in adults aged ≥18 years in the European Union and then, as of January 2021, in 47 countries, including the United States, Brazil and Japan.17-20 Based on an open-label phase 3 study in children/adolescents with HAE-1/2,21 the European indication was further extended in 2017 to include treatment of attacks in paediatric patients aged 2 to <17 years,22 providing an important treatment option for a population with limited access to therapies. Icatibant is administered subcutaneously, available as a prefilled syringe and licensed for self-administration by a patient/caregiver with appropriate training.23 As of July 2019, icatibant has been used in clinical practice to treat an estimated >620,000 attacks (estimated cumulative patient exposure; Takeda data on file).

The 2017 revision of the International World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) guideline for the management of patients with HAE outlines several recommendations for on-demand treatment of attacks, including guidance that all attacks be considered for on-demand treatment; attacks should be treated as early as possible with plasma-derived or recombinant C1-INH, icatibant or ecallantide; patients should have sufficient medication to treat two attacks and carry medication at all times; and patients should be taught to self-administer if they have appropriately licensed treatment. The final two recommendations facilitate early treatment of attacks, which is associated with improved treatment outcomes.1 The 2019 International/Canadian HAE guideline and 2020 US Hereditary Angioedema Association Medical Advisory Board guideline corroborate these recommendations and highlight the need for the provision of on-demand treatment, even with the use of recently approved long-term prophylaxis (LTP) options (which were not yet available when the WAO/EAACI guideline was previously updated/revised).23

Patient registries are a valuable data source that can increase the understanding of how therapies are utilized in routine clinical practice, and they provide insights on long-term effectiveness, tolerability and patient experience.24 In rare diseases, patient registries facilitate follow-up of larger/more diverse patient groups and for a substantially longer time period than controlled trial settings.25

The Icatibant Outcome Survey (IOS; NCT01034969) is an ongoing, international, prospective, observational registry for patients who have received ≥1 icatibant injection. IOS was initiated in 2009 to monitor effectiveness/safety of icatibant in routine clinical practice, in line with the principles of good pharmacovigilance practice. As of March 2019, 549 patients with HAE-1/2 from the IOS registry have been treated, of 5995 total attacks. The objectives of the current review are to describe key learnings from IOS over time.

### 1.1 IOS study design

From July 2009 to March 2019, 13 countries, including Australia, Austria, Brazil, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Spain, Sweden and the United Kingdom, had centres participating in IOS.26 IOS is conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines; all participating centres obtain approval from local ethics committees, and written informed consent is obtained from all patients or parents/guardians of paediatric patients.

IOS registry design has been previously described in detail.27-29 Briefly, patients with HAE who have received ≥1 dose of icatibant are eligible to enrol in the IOS registry. Where applicable, patients with HAE or other angioedema conditions may be enrolled irrespective of treatment with icatibant and/or other treatments. Information on baseline demographics/attack characteristics is collected upon enrolment, and attack-related frequency, severity and outcomes are recorded during regular patient follow-up visits (which optimally occur twice yearly). Icatibant treatment outcome measures include time to first administration of icatibant, time to attack resolution, total attack duration (Figure S2) and number of doses administered per attack. Safety was assessed via reporting of AEs/SAEs considered related to icatibant by investigators.

### 2 METHODS

This review article summarizes the previously published data on the key findings from IOS: the long-term effectiveness and safety of icatibant in real-world clinical practice; effectiveness of one icatibant dose in the treatment of HAE attacks; effects associated with early treatment and self-administration; and effectiveness/safety of icatibant across patient subgroups.
3 | TEN YEARS OF IOS EXPERIENCE WITH ICATIBANT IN ADULT AND PAEDIATRIC PATIENTS WITH HAE

3.1 | Characteristics of icatibant-treated attacks in patients with HAE-1/2 (July 2009–March 2019)

From July 2009 to March 2019, 1052 patients with HAE-1/2 enrolled in IOS (Table 1), including 39 paediatric patients. A total of 5995 reported attacks were treated with icatibant in 549 patients; 523 patients had available data for icatibant injection times/dates and attack characteristics. A mean 11.5 attacks per patient were treated with icatibant after IOS enrolment. The most common attack locations were abdominal (50.2%) and cutaneous (31.3%); 3.7% of attacks were laryngeal. Most attacks before treatment were moderate (43.6%) or severe/very severe (45.2%; Figure S3).

3.2 | Icatibant treatment outcome measures

The median time to attack resolution and attack duration for attacks treated with icatibant were 6 and 9 h respectively (Figure 1A; July 2009–March 2019).26 When stratified by time to treatment (median, <1 vs. ≥1 h), early treaters had a shorter median time to resolution and attack duration vs. late treaters (July 2009–October 2017; Figure 1B).

3.3 | Self-administration and effectiveness of one icatibant dose

The proportion of patients self-administering icatibant rose from 25.0% in 2009 to 96.2% in 2018 (Figure 2).26 Of 6507 icatibant-treated attacks in 554 patients with HAE-1/2 (July 2009–September 2019), a single icatibant dose was used to treat 92.9% of attacks. No additional use of C1-INH was reported for 91.6% of attacks treated with one icatibant injection. Only 7.1% of attacks required >1 icatibant dose; these were generally moderate or severe/very severe, with abdominal involvement.33

3.4 | Safety of icatibant treatment

Between July 2009 and March 2019, 618 total patients with HAE-1/2 received icatibant during follow-up. Of these, 24 (3.9%) reported 75 AEs considered by investigators as possibly or probably related to icatibant (Table 2).26 Of the 75 related AEs, most frequent were injection site erythema, asthenia and local hypersensitivity.26,34 There were six local hypersensitivity events, all of which were described as itching, burning and erythema on the abdomen after icatibant administration. None of the events were regarded as serious.34 SAEs considered by investigators as possibly related to icatibant were reported in two patients (0.3%), including one event each of gastritis and angioedema.35 No deaths have been reported from AEs that were considered icatibant related.26

3.5 | Icatibant use in paediatric patients with HAE-1/2

An analysis of IOS data from July 2009 to January 2019 compared patient characteristics and treatment outcomes in 11 paediatric and 569 adult patients who had received icatibant to treat attacks.36 Baseline demographics/attack characteristics are shown in Table S1. Icatibant treatment outcomes were comparable among the paediatric and adult cohorts (Figure 3). The safety profile of icatibant in paediatric and adult patients is shown in Table S1. Among paediatric-treated patients, there were no recorded AEs/SAEs considered icatibant-related.36

3.6 | Icatibant treatment of attacks in patients with HAE nC1-INH

Bradykinin may play a role in angioedema attacks in some patients with HAE nC1-INH. There is consensus-level evidence in the HAE Canadian/International guideline, based on small non-controlled studies, to recommend icatibant for attacks in these patients.23,37 An earlier analysis was conducted in 22 IOS patients in France with HAE nC1-INH (July 2009–September 2013).38 Across all IOS countries (July 2009–January 2020), 212 patients with HAE nC1-INH have been enrolled (Table S2); 514 attacks in 80 patients were treated with icatibant, with 91.0% receiving one injection. Of attacks with known severity, 85.2% were severe/very severe. For 489 attacks with data, median (range) time to treatment, time to resolution and attack duration were 1.2 (0–96.0), 8.5 (0–98.3) and 12.7 (0.3–99.0) h respectively. The safety profile in patients with HAE nC1-INH is shown in Table S2.39
4. **KEY LEARNINGS FROM THE IOS REGISTRY**

4.1 **Comparable icatibant effectiveness in a real-world setting and efficacy in clinical trials, with one icatibant dose effective for the vast majority of attacks**

A study evaluating non-laryngeal attacks in IOS (July 2009–March 2013) versus attacks in the controlled FAST-3 trial indicated that the efficacy of icatibant in a controlled setting was maintained in clinical practice. Mean time to a healthcare professional (HCP)-administered treatment was significantly shorter in IOS than in FAST-3 (2.7 vs. 7.1 h; \( p < .001 \)). This may be partially attributed to the requirement for attacks to be moderate/severe before receiving HCP-administered icatibant in FAST-3, leading to a longer time between symptom onset and treatment administration. Although definitions differed slightly, the mean time to resolution with HCP administration was 7.9 h in IOS and 28.3 h in FAST-3 (\( p < .001 \)), and attack duration was 10.8 and 35.4 h respectively (\( p < .001 \)). Outcomes with HCP-/self-administered icatibant in IOS were also shorter than with HCP-administered treatment in FAST-3. Again, this may be because of the longer time to treatment in FAST-3.

IOS data were used to evaluate icatibant treatment of 67 laryngeal attacks in 42 patients in a real-world setting (September 2008–May 2013). One icatibant dose was used to treat 87.9% of attacks, comparable with controlled trials; icatibant was self-administered for 62.3% of attacks. Median time to first icatibant administration, time to attack resolution and total attack duration were 2, 6 and 8.5 h respectively. In contrast, the median attack duration of 24 untreated laryngeal attacks was 48 h. Although the 2012 WAO guideline recommended that intubation or tracheotomy should be considered early in the presence of progressive upper airway oedema, a notable addition to the 2017 revision was the suggestion that rapid treatment of laryngeal attacks with effective on-demand treatment is essential. This analysis provided further evidence supporting icatibant as first-line treatment for laryngeal attacks.

An analysis of icatibant-treated attacks that also included the year before IOS enrolment (February 2008–December 2012) was used to evaluate the effectiveness of one dose of icatibant. Of 652 attacks, 528 (81.0%) were treated and resolved with a single dose of icatibant. The remaining 124 (19.0%) attacks were treated with one or more injections of icatibant and/or C1-INH rescue medication.

4.2 **Outcomes of early treatment with icatibant facilitated by self-administration**

Although the 2012 WAO guideline recommended early treatment of attacks, there was limited strong supporting evidence at the time. The first publication of IOS data (July 2009–February 2012) reported an analysis of 426 attacks in 136 patients, demonstrating that early treatment with icatibant resulted in faster resolution and shorter duration of HAE attacks. Mean time to resolution and attack duration were significantly shorter for attacks treated \(< 1 \text{ h} \) vs. \( \geq 1 \text{ h} \) after symptom onset (5.8 vs. 8.8 h \([ p = .033 ] \) and 6.1 vs. 16.8 h \([ p < .001 ] \), respectively). The analysis also highlighted that treatment \(< 1 \text{ h} \) after onset was more likely to occur with self-administration than HCP administration (44.0% vs. 22.0%; \( p = .001 \)), and attacks receiving self-administered icatibant were shorter than those receiving HCP-administered icatibant (\( p < .05 \)).

Although post-hoc analyses of clinical trial data for other on-demand medications had reported benefits of early treatment,
this IOS analysis provided valuable insights into the correlation between treatment time and outcomes in a large real-world cohort. The 2017 WAO/EAACI guideline now strongly recommends treating attacks as early as possible, irrespective of medication type, with supporting evidence that includes these findings.1

Despite the 2012 WAO guideline suggesting that all patients with HAE-1/2 should be considered for home therapy and self-administration,42 opportunities for patients to self-treat attacks at that time were limited by the availability of only intravenous C1-INH and variable licensing for icatibant.47 Based on the phase 3b open-label EASSI study,48 the European label for icatibant was revised in 2011 to include the option for self-administration,49 in accordance with the U.S. Food and Drug Administration’s approval that year.17

An analysis of 652 icatibant-treated attacks in 170 patients from IOS (February 2008–December 2012) confirmed that self-administration of icatibant provided greater treatment benefits.50 Of 431 self-treated attacks (66.1% of all attacks), 400 were treated via self-injection by the patient and 31 via injection by another non-HCP individual. The proportion of patients who chose self-administration increased from 40.3% in 2009 to 89.7% in 2012. Although no significant difference in median time to resolution was observed between self-treated and HCP-treated attacks, early treatment was associated with shorter time to resolution, irrespective of administration type (p < .05), and median time to administration was significantly shorter for self-treated attacks (1.5 vs. 2.4 h; p = .016).

The 2017 revision of the WAO/EAACI guideline assigned a grade C level of evidence (comparative trial with methodological limitations or large retrospective observational studies) for the recommendation for self-administration from a grade D recommendation in 2012 (adapted from existing consensus documents or based on expert opinion voting).1,42

4.3 | Safety data from icatibant use over time in routine clinical practice

Six years of data (July 2009–February 2015) were used for the first analysis of the long-term safety of icatibant in all treated patients (n = 557) in IOS, irrespective of diagnosis (HAE or other angioedema conditions).35 Seventeen patients (3.1%) reported 43 AEs considered by investigators as possibly or probably treatment related. Injection site erythema (six events [14.0%] in one patient) was among the most frequent related AEs. This analysis of a large real-world cohort showed a lower reported occurrence of local injection site reactions than in controlled clinical trials.

4.4 | Icatibant use across a variety of subgroups of patients with HAE-1/2, including patients aged ≥65 years

A major advance in the management of patients with HAE-1/2 has been the development of targeted LTP therapies to prevent or attenuate attacks.1,23 However, patients receiving any type of LTP should remain aware of the possibility of breakthrough attacks and have access to on-demand treatment.23

An analysis of IOS data (July 2009–February 2016) evaluated icatibant treatment patterns/outcomes for breakthrough attacks in patients receiving LTP55 (based on LTP options available at the time, agents that are now recommended as first-line treatments, lanadelumab and subcutaneous C1-INH, were not approved).23 Of 3228 attacks, 973 (30.1%) occurred in 171 patients during LTP use. Androgens were the most commonly used LTP medication (108/171; 63.2%), followed by tranexamic acid (43/171; 25.1%) and intravenous C1-INH (15/171; 8.8%). The frequency of attacks (for each LTP type) was calculated by dividing the number of attacks by the total treatment duration. Patients on LTP experienced an average of 1.5–2.3 attacks per year (depending on LTP type) vs. two attacks per year in patients without LTP. One icatibant dose was used to treat 82.5% of attacks with LTP and 82.8% of attacks without LTP. There were no significant differences in median time to treatment, time to resolution or attack duration with and without LTP use.

A comparison of attacks in 342 patients by body mass index category at baseline (July 2009–February 2016) provided insight into a potential relationship between body weight and attack characteristics.52 After icatibant treatment, time to attack resolution and total

FIGURE 2 Type of icatibant administration by year for treated hereditary angioedema (HAE) attacks in patients with HAE type 1 or 2 (July 2009–March 2019). Note: for the year 2019, data shown are through March 31. Attacks for which method of icatibant administration was not reported were excluded. HCP, healthcare professional.
TABLE 2 Summary of TEAEs considered possibly or probably related to icatibant in patients with HAE-1/2 by System Organ Class and Preferred Term (July 2009–March 2019)\textsuperscript{30}

| TEAEs considered related to icatibant | Patients, n (%) | Events, n (%) |
|--------------------------------------|----------------|--------------|
| Any related TEAE                     | 24 (3.9)       | 75 (100)     |
| Related TEAEs (>1 event by preferred term) |                |              |
| General disorders and administration site conditions |                |              |
| Injection site erythema              | 11 (1.8)       | 22 (29.3)    |
| Application site erythema            | 3 (0.5)        | 3 (4.0)      |
| Pain                                 | 3 (0.5)        | 3 (4.0)      |
| Application site pain                | 2 (0.3)        | 3 (4.0)      |
| Drug ineffective                     | 2 (0.3)        | 2 (2.7)      |
| Infusion site pain                   | 2 (0.3)        | 2 (2.7)      |
| Asthenia                             | 1 (0.2)        | 7 (9.3)      |
| Administration site reaction         | 1 (0.2)        | 4 (5.3)      |
| Gastrointestinal disorders           |                |              |
| Gastritis                            | 1 (0.2)        | 3 (4.0)      |
| Investigations                       | 1 (0.2)        | 4 (5.3)      |
| Vascular disorders                   |                |              |
| Hyperaemia                           | 3 (0.5)        | 4 (5.3)      |
| Immune system disorders              |                |              |
| Hypersensitivity                     | 1 (0.2)        | 6 (8.0)      |
| Serious TEAEs considered related to icatibant |            |              |
| Any serious related TEAE             | 2 (0.3)        | 2 (100.0)    |
| Gastrointestinal disorders           |                |              |
| Gastritis                            | 1 (0.2)        | 1 (50.0)     |
| Skin and subcutaneous disorders      |                |              |
| Angioedema\textsuperscript{a}        | 1 (0.2)        | 1 (50.0)     |
| TEAEs leading to death related to icatibant | 0             | 0            |

Abbreviations: HAE-1/2, hereditary angioedema type 1 or 2; TEAE, treatment-emergent adverse event.

\textsuperscript{a}Two doses of icatibant were administered before this patient was hospitalised for 24 h. In the hospital, fresh-frozen plasma was given, and the patient was discharged the following day without any sequelae.

attack duration were significantly shorter for patients in the overweight (p < .001 for both) and obese (p = .021 and p = .025, respectively) categories vs. patients in the normal BMI category. This may reflect that time to treatment was shorter for patients who were overweight (p = .007) or obese (p = .385) vs. patients with normal weight.

Analyses of clinical characteristics/safety data in elderly (aged ≥ 65 years; n = 100) vs. younger patients (aged < 65 years; n = 772; July 2009–February 2018) revealed significant differences in median age at symptom onset (17 vs. 12 years, respectively; p = .0001) and at diagnosis (41 vs. 19.4 years, respectively; p < .0001) and time to diagnosis (23.9 vs. 4.8 years, respectively; p < .0001).\textsuperscript{53} Additionally, elderly patients were more likely than younger patients to have comorbidities and to be receiving concomitant medications for cardiovascular/cerebrovascular conditions. Icatibant treatment of at least one attack was recorded for 63.0% of elderly and 66.2% of younger patients, and proportions of elderly vs. younger patients experiencing AEs possibly or probably related to icatibant were comparable (2.0% vs. 2.7%, respectively). There were no icatibant-related SAEs in elderly patients and three icatibant-related SAEs in younger patients (previously described).

4.5 The diagnostic journey and triggers/prodromal symptoms experienced by patients with HAE-1/2

The first IOS analysis evaluating patients’ diagnosis journeys (171 patients; July 2009–June 2012) found a median (range) time between HAE onset and diagnosis of 8.5 (0–62) years.\textsuperscript{54} Time to diagnosis was shortest in Germany (2 years) and longest in Italy (15 years), although differences between countries were not statistically significant.

A later analysis of trends over time (July 2009–January 2017) included 250 patients born before 1990 and diagnosed before aged 25 years.\textsuperscript{55} Over time, lower age at diagnosis (p < .0001; r = −0.2659) and shorter time to diagnosis (p = .0029; r = −0.1874) were observed; patients born between 1950 and 1960 reported a delay of 7 years, vs. 1.4 years for patients born between 1980 and 1990. Patients with a family history of HAE-1/2 had a shorter time to diagnosis than those without (2 vs. 5.6 years; p = .0092).

In an analysis of misdiagnosis trends (July 2009–January 2016), 185/418 patients (44.3%) with data received at least one misdiagnosis before a correct diagnosis of HAE-1/2.\textsuperscript{56} The most common misdiagnoses were allergic angioedema (55.7%) and appendicitis (27.0%). Patients with misdiagnoses reported a significantly longer median time to HAE-1/2 diagnosis than those without (13.3 vs. 1.4 years for patients born between 1950 and 1960; p < .0001) and less likely to have a family history of HAE-1/2 (41.6% vs. 65.5%; p < .001).

Data from IOS were also used to identify physician specialties involved in diagnosing HAE-1/2 (July 2009–January 2017).\textsuperscript{57} Of 471 patients with data, 395 (83.9%) were diagnosed by a specialist; most frequent were allergists (35.2%), clinical immunologists (21.8%) and dermatologists (19.2%). Despite HAE onset often occurring in childhood/adolescence,\textsuperscript{58} paediatricians and paediatrician immunologists diagnosed only 3.0% and 2.5% of cases respectively. Of patients diagnosed by specialists, the median time to diagnosis was shortest for those diagnosed by paediatricians (1.1 years; n = 12) and longest for diagnosis by clinical immunologists (12 years; n = 86); known family history reduced the time to diagnosis by paediatricians vs. none/unknown history (0.79 vs. 7.05 years). Delays associated with disease specialists may be a consequence of referrals occurring late in patients’ diagnostic journeys.
An analysis of 395 patients investigated potential triggers and prodromes (July 2009–April 2015). An identifiable trigger was reported for 22.6% of attacks; the most common triggers after IOS enrolment were emotional distress (33.0% of patients), physical trauma (12.0% of patients), change in oestrogen levels in females (11.0% of patients) and infection (10.0% of patients). Prodromal symptoms were reported for 23.4% of attacks; the most common after IOS enrolment were emotional distress (33.0% of patients), physical trauma (12.0% of patients), tiredness (17.0% of patients) and tight or prickling sensation of the skin (14.0% of patients).

4.6 | Differing patient journeys, treatment behaviours and icatibant treatment outcomes in patients with HAE

Data from 481 patients with HAE type 1/2 across six European countries (Austria, France, Germany, Italy, Spain and United Kingdom; July 2009–April 2015) showed a wide variation in the median number of attacks per year at baseline (3.6 [France] to 18 [Germany–Austria]; \( p < .001; n = 325 \)).\(^{29}\) Self-administration of icatibant at the time of analysis varied from 70.9% in Spain to 94.6% in the United Kingdom. There were significant differences \( (p < .001) \) in median time to treatment (0 [Germany–Austria] to 4.4 [France] h), time to resolution (3 [Germany–Austria] to 12 [France] h) and attack duration (3.1 [Germany–Austria] to 18.5 [France] h). Earlier treatment was associated with improved outcomes, confirming previous findings.

In Israel (\( n = 58; \) July 2009–July 2016), compared with other countries (\( n = 594 \)), there was a lower median age at diagnosis (16.7 vs. 21.3 years; \( p = .036 \)) and shorter time from symptom onset to diagnosis (0.8 vs. 6.6 years; \( p = .025 \)).\(^{29}\) Patients in Israel were more likely to self-administer (97.2% vs. 87.5%; \( p = .003 \)) and had shorter attack duration (median, 5 vs. 9 h; \( p = .026 \)); however, they had more untreated attacks during the follow-up period (median, 5 vs. 1; \( p = .036 \)).

In the United Kingdom (\( n = 58; \) February 2008–July 2016), compared with other countries (\( n = 436 \)), there was a higher proportion of self-treated attacks (95.8% vs. 86.6%; \( p < .001 \)) but no significant differences in treatment outcomes.\(^{60}\)

In Germany (\( n = 93; \) July 2009–January 2017), compared with other countries (\( n = 592 \)), patients reported fewer severe/very severe attacks (38.7% vs. 57.5%; \( p < .001 \)), and a greater proportion of attacks were treated with one dose of icatibant (97.1% vs. 91.6%; \( p = .0003 \)).\(^{41}\) German patients reported a shorter median time to treatment (0 vs. 1.5 h), time to resolution (3 vs. 7 h) and attack duration (4.3 vs. 10.5 h; \( p < .0001 \) for all). In addition to improved outcomes, early treatment may have resulted in fewer severe/very severe attacks, with attacks treated before severity progressed.

5 | LIMITATIONS AND VALUE OF THESE ANALYSES

These analyses may be limited by missing/incomplete data, potential selection bias and suboptimal longitudinal retention. Data derived from patient recall and treatment outcomes can be reliant on patient interpretation. Analyses that used retrospective attack data from earlier than July 2009 (registry initiation) may have been subject to greater recall bias. Data on attacks treated with on-demand medications other than icatibant were not routinely collected. Data on the use of icatibant to treat breakthrough attacks in patients using recently approved LTP options (e.g. lanadelumab and subcutaneous C1-INH) are currently scarce but will increase over time. Although icatibant was approved in some countries for use in paediatric patients aged 2 to <18 years in 2017, patients enrolled before this label extension were all adults, and retrospective data on diagnostic delays may be subject to recall bias. To date, comparison of icatibant efficacy in patients <65 years old with patients ≥65 years has not been published.

Despite these limitations, registries provide important insights into the effectiveness/safety of treatments in uncontrolled settings.
Future analyses from existing registries may provide valuable insights into the use of icatibant for on-demand treatment for breakthrough attacks in patients receiving recently approved therapies for LTP; a recent randomised controlled trial reported that icatibant was used by patients treated with lanadelumab for attack prevention.62

6 | CONCLUSIONS

Data collected in IOS over 10 years have helped inform clinical strategies/guidelines to optimise disease management and limit disease burden.

Although advances continue to be made in developing increasingly effective and convenient LTP options, the continual risk of breakthrough attacks means that patients should always have access to effective on-demand treatment. Findings from 10 years of registry experience demonstrate consistent effectiveness/tolerability of icatibant over an extensive time period, an important consideration given the recurrent nature of HAE attacks. There were no treatment-related deaths, and the most frequent adverse events related to icatibant treatment were injection site erythema, asthenia and local hypersensitivity.

AUTHOR CONTRIBUTIONS

IA contributed to study design of the IOS. JB participated in data acquisition. All authors participated in data analysis and/or interpretation, participated in drafting the manuscript or revising it for critically important intellectual content, and approved the final draft.

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CONFLICT OF INTEREST

MM is or recently was a speaker and/or advisor for BioCryst, CSL Behring, KalVista, Moxie, Pharmac, Pharvaris and Takeda; and has received research funding from BioCryst, CSL Behring, Moxie, Pharmac and Takeda. WA is a member of advisory boards and speaker bureaus for BioCryst, CSL Behring, Pharmac and Takeda; has received research grants from CSL Behring and Takeda; has received funding to attend conferences/educational events and donations to the departmental fund from Takeda; and is/or has been a clinical trial investigator for BioCryst and Takeda. TC is a member of advisory boards for BioCryst, CSL Behring, Novartis, Octapharma, Pharmac and Takeda; is a member of speaker bureaus for CSL Behring, Novartis and Takeda; has received grants or honoraria from BioCryst, CSL Behring, Novartis and Takeda; has received funding to attend conferences/educational events from CSL Behring, Novartis, Pharmac and Takeda; is/or has been a clinical trial registry investigator for BioCryst, CSL Behring, Novartis, Pharmac and Takeda; and is a researcher from the IdiPAZ programme for promoting research activities. LB has received honoraria from BioCryst, CSL Behring, Novartis, Pharmac and Takeda; and her institute has received research funding from CSL Behring, GlaxoSmithKline, Novartis, Roche and Takeda. ASG has been a speaker or consultant for BioCryst, Biotest, CSL Behring and Takeda, and received a grant of researcher initiative from Takeda. JB and IA are employees of Takeda and hold stock/stock options in Takeda. HJL has received research grant support and/or speaker/consultancy fees from Adverum, BioCryst, CSL Behring, GlaxoSmithKline, Intellia, Octapharma, Pharmac, Pharvaris and Takeda. Her current affiliation is with Auckland District Health Board, New Zealand.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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