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# Introduction

- Hereditary angioedema (HAE) is a rare and potentially lifethreatening genetic disease characterized by recurrent episodes of swelling. Attacks are painful and can have a significant adverse impact on patients' quality of life<sup>1-3</sup>
- Clinical practice guidelines recommend the use of shortterm prophylactic (STP) therapy prior to medical or dental procedures in patients with hereditary angioedema (HAE)<sup>4,5</sup>
- Plasma-derived C1 esterase inhibitors (C1-INH) are the firstline therapy in this setting, but the quality of evidence for this recommendation is moderate or low<sup>4,5</sup>
- All recommended STP treatments require parenteral administration, which presents significant challenges related to preparation, venous access, injection-site-associated pain, and discomfort<sup>6,7</sup>
- There remains an unmet need for a safe and effective oral STP option for HAE
- To inform the design of a trial to assess STP with an ondemand therapy, we performed a targeted literature search to characterize the evidence for the existing treatments and to identify ongoing clinical trials evaluating agents for use as STP therapy in HAE

- A targeted literature review was performed by a PubMed search based on a predefined search string to identify all studies that discussed STP in HAE in the preprocedural setting, including before dental, medical, or surgical events
- Search string: (((((hereditary angioedema)) AND ((prophylaxis)))) AND ((((preprocedural) OR (short-term)))) AND (surgical OR medical OR dental)
- Filters: English; from 2000-2022
- Additional candidate publications were gathered from citation searches
- Selection of eligible publications were defined by type of primary study (included: prospective trial, retrospective study, registry analysis; excluded: case study, case series, reviews, crosssectional surveys, guidelines, other) and the presence of STP outcome data (eg, HAE attack rate after preprocedural STP)
- A database search of ClinicalTrials.gov was performed to identify ongoing clinical trials of STP in HAE
- Search string: Condition or disease = "Hereditary Angio-Edema"; Other terms = "Short-term OR preprocedural OR preprocedure"
- All data were analyzed descriptively using MS Excel software (Microsoft, Redmond, WA, US)

**Disclosures** 

Medical writing assistance was provided under the direction of the authors by Katherine Stevens-Favorite, PhD, of Cadent, a Syneos Health group company, and was supported by KalVista Pharmaceuticals. Inc.

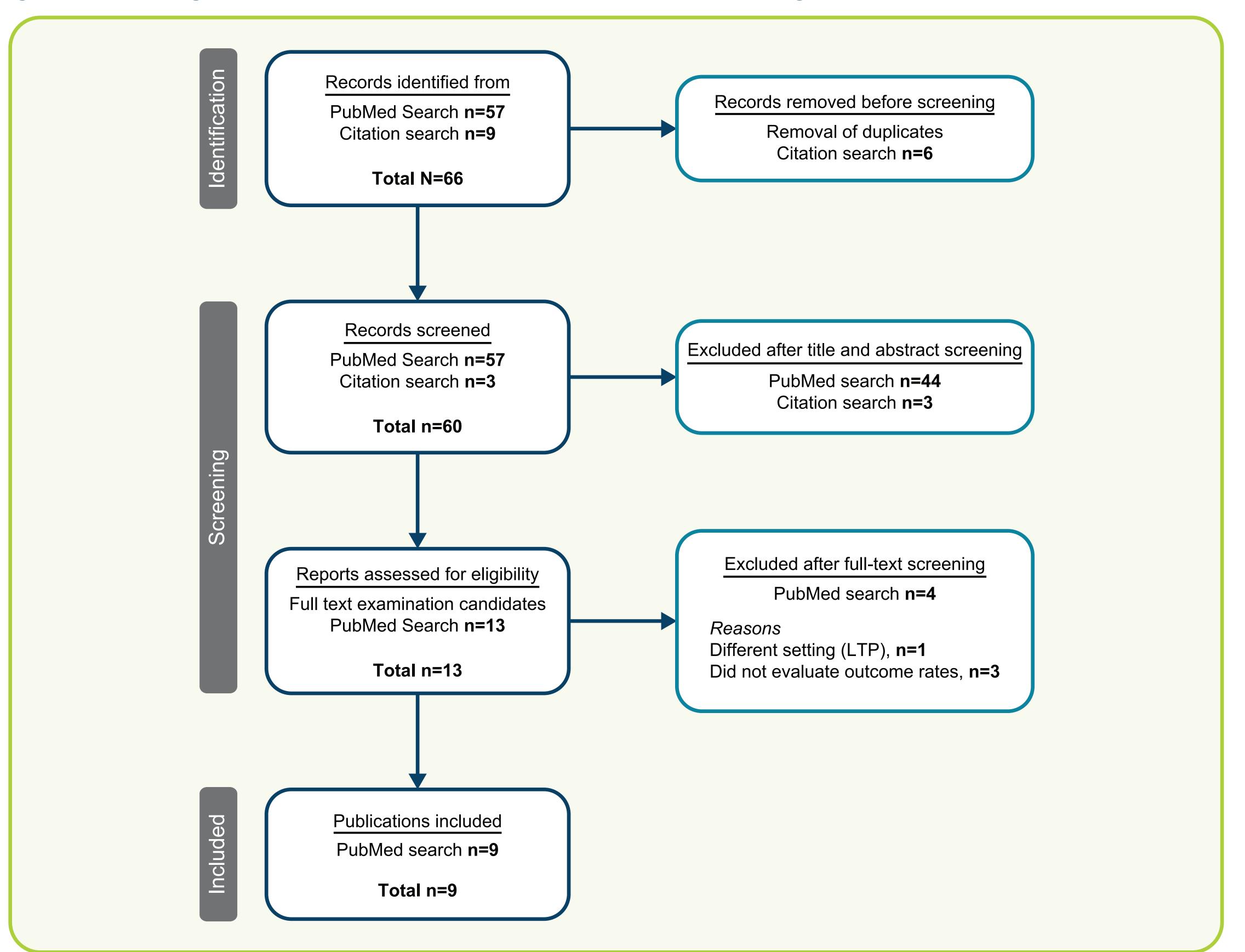
Association. PKA, MDS, and CMY are employees of KalVista Pharmaceuticals.

Presented during the Western Society of Allergy, Asthma and Immunology (WSAAI) 60th Annual Scientific Session, February 5-9, 2023, Kamuela, HI, US.

### A flow diagram of the search output is presented in Figure 1

- The output of the PubMed search string was 57 individual articles
- − The most common article type in the search output was review (n=23), followed by primary study in STP (n=8), case series (n=9), case study (n=9), and other article types (n=8)
- One case series with a large sample size was included in the targeted literature review set<sup>8</sup>
- A citation search of studies that support recommended preprocedural STP agents in the current guidelines<sup>4,5</sup> was performed to supplement the PubMed search (n=9)

Figure 1. Flow Diagram for the Identification of Studies for Inclusion in Targeted Literature Review



## LTP, long-term prophylaxis

- Nine studies evaluating STP therapy prior to invasive or medical procedures were identified, including eight retrospective analyses of either medical records (n=7) or clinical trial data (n=1), and one patient registry (**Table 1**)<sup>8-16</sup>
- The study designs and treatment patterns were heterogeneous between studies
- Only two studies prospectively collected data: the registry analysis and one survey conducted after a chart review<sup>10,15</sup>
- A summary of evaluated outcomes from these studies is shown in Table 2. All suggested benefit from STP with C1-INH prior to invasive procedures

## Table 1. Characteristics of Included Studies

First Author (year)	Study Design	Intervention	History	Efficacy Outcomes	Study Characteristics	Grade
Bork K et al, 2012	Retrospective	• C1-INH concentrate	Dental	<ul> <li>HAE attack rate with STP</li> <li>HAE attack rate without STP</li> </ul>	<ul> <li>All dental procedures were tooth extractions</li> <li>2 doses of C1-INH concentrate were evaluated</li> <li>AE incidence was collected</li> </ul>	С
Farkas H et al, 2012	Retrospective, prospective	<ul><li>Danazol</li><li>Tranexamic acid</li><li>C1-INH concentrate</li></ul>	Dental, medical, surgical	HAE attack rate     with STP	<ul> <li>How STP agent was selected for each patient was unclear</li> <li>AE incidence was collected</li> </ul>	C
Grant JA et al, 2012	Retrospective	• C1-INH-nf	Dental, medical, surgical	HAE attack rate     with STP	<ul> <li>Patients were participants in placebo-controlled RCT and subsequent OLE</li> <li>There were no preplanned formal assessments of STP effectiveness</li> <li>AE incidence was collected</li> </ul>	C
Jurado-Palomo J et al, 2012	Retrospective	<ul><li>Danazol</li><li>Stanozolol</li><li>C1-INH concentrate</li></ul>	Dental	<ul> <li>HAE attack rate with STP</li> <li>HAE attack rate without STP</li> </ul>	<ul> <li>All patients at single institution in 13 years</li> <li>AE incidence was collected</li> </ul>	D
Gavigan G et al, 2014	Retrospective	C1-INH concentrate	Childbirth, dental, invasive procedure, surgical	HAE attack rate     with STP	<ul> <li>All patients at single institution in 16 years</li> <li>Prespecified primary outcome: number of postprocedural HAE attacks after STP administration of C1-INH concentrate</li> </ul>	D
Gonzalez-Quevedo T et al, 2016	Retrospective	• pdhC1-INH	Medical	<ul> <li>HAE attack rate with STP</li> <li>HAE attack rate without STP</li> </ul>	<ul> <li>Patients during pregnancy and childbirth at 5 HAE reference hospitals</li> <li>AE incidence was collected</li> </ul>	D
Magerl M et al, 2017	Patient registry	C1-INH concentrate	Dental, medical	<ul><li>STP use rate</li><li>HAE attack rate with STP</li></ul>	<ul> <li>Analysis of STP usage in Berinert Registry conducted between 2010 and 2014</li> <li>AE incidence was collected</li> </ul>	С
Valerieva A et al, 2020	Retrospective	• rhC1-INH	Medical, stressful life events	<ul> <li>HAE attack rate with STP</li> <li>HAE attack rate without STP</li> </ul>	<ul> <li>A large case series with records from 7 countries</li> <li>AE incidence was collected</li> </ul>	D
Zanichelli A et al, 2020	Retrospective	<ul><li>C1-INH concentrate</li><li>Danazol</li></ul>	Dental	<ul> <li>HAE attack rate with STP</li> <li>HAE attack frequency before and after dental care</li> </ul>	<ul> <li>All patients at a single institution for 8 years</li> <li>Prespecified primary endpoints: <ol> <li>% of patients encountering hurdles in access to dental care</li> <li>% of procedures followed by postprocedural attacks in patients receiving and not receiving a prophylaxis for angioedema</li> </ol> </li> </ul>	D

Results

human C1-INH; STP, short-term prophylaxis.

• The search output included two studies that supported label expansion in the EU for C1-INH to permit use for STP in patients with HAE<sup>9,11,17-19</sup>

 Bork et al (2011) performed a retrospective study of STP with C1-INH, in which there were four HAE attacks after 53 tooth extractions (7.5%) with STP compared with 124 attacks after 577 tooth extractions without STP (21.5%; P<0.035)9

- In another retrospective study, Grant et al (2012) reported that 91 doses of nanofiltered C1-INH were administered as preprocedural prophylaxis to 41 patients with HAE who were participants in a placebo-controlled trial (n=7) and/or its open-label extension trial (n=36); for 89/91 (98%) procedures, there was no HAE attack within 72 hours<sup>11</sup>
- Three studies were in the output from ClinicalTrials.gov, and one was excluded because it does not assess STP outcome data (Table 3)<sup>20-22</sup> There were no ongoing clinical studies evaluating STP for HAE

## Table 2. STP Use and Postprocedural HAE Attack Outcomes in Included Studies

First Author (year)	N	Age (y)	Male/ Female (n)	Procedures (n)	Findings	Statistical Analysis
Bork K et al, 2012	171	Mean: 43.6 SD: 15.1	68/103	705	<ul> <li>128/705 dental, diagnostic, or surgical interventions were performed with STP</li> <li>16 HAE attacks occurred in 128 (12.5%) procedures with STP</li> <li>124 HAE attacks occurred after 577 (21.5%) procedures without STP</li> </ul>	<ul> <li>The rate of attacks was significantly different between patient groups (χ²<sub>(2)</sub>=6.71; P=0.035)</li> </ul>
Farkas H et al, 2012	137	Children (n=20) Mean: 12.2 Range: 2.2-17.3 Adults (n=117) Mean: 41.3 Range: 18.5-81.2	60/77	134	<ul> <li>134/134 procedures were performed with STP</li> <li>13 HAE attacks occurred in 134 procedures with STP (2 children and 7 adults)</li> <li>HAE attacks occurred <ul> <li>Danazol: 36% (5/14)</li> <li>Tranexamic acid: 50% (3/6)</li> <li>C1-INH concentrate: 9% (5/54)</li> </ul> </li> </ul>	<ul> <li>C1-INH concentrate         was associated with         significantly fewer HAE         attacks compared with         danazol (P=0.0254,         Fisher's exact test) and         compared with danazol         and tranexamic acid         (P=0.0064, x² test)</li> </ul>
Grant JA et al, 2012	41	Mean: 37 Range: 6-80	10/31	91	• 2 HAE attacks after 91 (2.2%) procedures with STP	
Jurado-Palomo J et al, 2012	24	Median: 44.1 Range: 29.5-55.9	10/14	66	C1-INH concentrate was administered as an STP for 42/66 procedures	<ul> <li>Association between mild postprocedural upper airway angioedema and lack of preprocedural C1-INH concentrate (P=0.019, Fisher exact test)</li> </ul>
Gavigan G et al, 2014	12	Mean: 42 Range: 19-62	4/8	24	0 HAE attacks after 24 procedures	
Gonzalez-Quevedo T et al, 2016	61	Mean: 27.1 <sup>a</sup> Range: 16-42	0/61	111	<ul> <li>0 attacks after 14 deliveries completed with STP</li> <li>Mild local HAE symptoms were observed in 6/111 deliveries completed without STP (5.4%)</li> </ul>	
Magerl M et al, 2017	318	Mean: 42.4 Range: 8-76	Female: 74.7%	N/A	<ul> <li>79/318 participants reported ≥1 use of C1-INH concentrate as STP</li> <li>Cumulative HAE attack rate within 1 and 2 days after STP was .04 (95% CI, .015088) and .06 (95% CI, .028115) attacks per infusion</li> </ul>	
Valerieva A et al, 2020	51	Median: 44 Range: 17-73	19/32	70	<ul> <li>70 procedures were performed with STP</li> <li>2 HAE attacks after 70 (2.9%) procedures in procedures performed with STP</li> </ul>	
Zanichelli A et al, 2020	29	Median: 45 IQR: 24-53 Range: 8-85	14/15	75 (n=20 pts)	<ul> <li>60/75 dental procedures were performed with STP</li> <li>0 HAE attacks after 60 procedures performed with STP</li> <li>1 HAE attack occurred in a procedure without STP</li> </ul>	

### Table 3. Study Characteristics of ClinicalTrials.gov Output

Registry Identifier	Study Design	Reported Enrollment	Status	Intervention	STP Outcome(s)
NCT01541423	Patient registry	83	Complete	C1-INH-nf	<ul> <li>Not stated</li> </ul>
NCT01034969	Patient registry	3000	Recruiting	Icatibant; C1-INH-nf	<ul> <li>Drug exposure data for preprocedural treatments with C1-INH-nf; outcome of HAE attacks with treatment with C1-INH-nf</li> </ul>

C1-INH-nf, nanofiltered C1 esterase inhibitor; HAE, hereditary angioedema; STP, short-term prophylaxis

# Conclusions

- Our literature review confirms that there are few prospective and no controlled studies in the short-term prophylaxis setting that support the present first-line treatment options for preprocedural prevention of acute HAE attacks
- Consistent with prior studies, therefore, we have designed a 2-year, open-label, phase 3 extension trial (KONFIDENT-S, NCT05505916), which will evaluate the safety of sebetralstat, an investigational oral plasma kallikrein inhibitor for the on-demand treatment of HAE attacks,<sup>23</sup> while also prospectively evaluating the effectiveness and safety of sebetralstat in the preprocedural STP setting<sup>24</sup>
- KONFIDENT-S is the first prospective trial that will evaluate an oral on-demand therapy for STP

- MAR has received research grants from BioCryst, CSL Behring, Ionis, KalVista, Pharvaris; consulted for BioCryst, Biomarin, CSL Behring, Cycle Pharma, Fresenius-Kabi, Ionis, KalVista, Pfizer, Pharming, Pharvaris, RegenexBio, Regeneron, Shire/Takea, and Spark; and provided speaker presentations for CSL Behring, Grifols, Pharming, and Shire. JAB has received speaker or consultancy fees from or served as a principal investigator for KalVista, Celldex, Pharvaris, Biomarin, Amgen, Allakos, CSL Behring, Shire, Pharming, BioCryst, AstraZenca, Sanofi-Regeneron, Novartis, and Genentech. WRL is a member of advisory boards for BioCryst, CSL Behring and Takeda; has received research grants from BioCryst, CSL Behring, Fresenius Kabi, Pharming and Takeda; payments for lectures from CSL Behring, Pharming, and Takeda; and is an advisory board member of the US Hereditary Angioedema
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