Oral Sebetralstat for On-Demand Treatment of Hereditary Angioedema: Phase 3 KONFIDENT Trial Results

Danny M. Cohn, MD, PhD
Amsterdam University Medical Center, University of Amsterdam, Amsterdam, Netherlands

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Disclosures

- Danny M. Cohn has received consulting fees paid to the institution, honoraria paid to the institution, meeting/travel support, research support, and/or served on advisory boards from KalVista Pharmaceuticals, Astria, BioCryst, CSL Behring, Intellia, Ionis Pharmaceuticals, Pharming, Pharvaris, and Takeda and serves a leadership role in the HAE International (HAEi) Medical Advisory panel for Central Eastern Europe and Benelux

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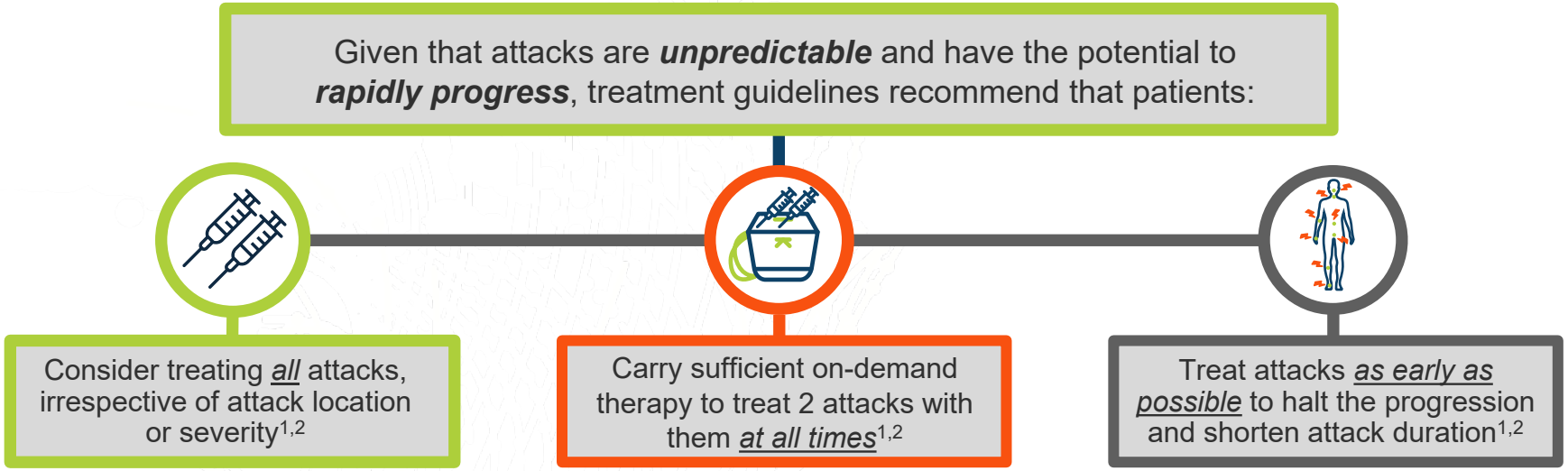
Background



- All currently approved therapies for on-demand treatment of HAE-C1INH attacks must be administered parenterally and are associated with delays and/or withholding of treatment[1,3-8]
- Sebetralstat, a plasma kallikrein inhibitor, is the first orally administered therapy being investigated in a phase 3 trial for the on-demand treatment of HAE-C1INH attacks[9]

HAE-C1INH, hereditary angioedema due to deficiency or dysfunction of C1 protein

1. Busse PJ, et al. *J Allergy Clin Immunol Pract.* 2021;9(1):132-150. 2. Maurer M, et al. *Allergy*. 2022;77(7):1061-1990. 3. Maurer, M et al. *PLoS One*. 2013;8(2):e5377 4. Beyaz S, et al. *Allergy Asthma Proc.* 2022;43(2):148-154. 5. Zanichelli A, et al. *Allergy*. 2015;70(12):1553-1558. 6. Federici C, et al. *BMJ Open*. 2018;8(7):e022291. 7. Banerji A, et al. *Allergy Asthma Proc*. 2015;36(3):213-217. 8. Mendivil, J, et al. *Orphanet J Rare Dis*. 2021;16(1):94. 9. Cohn DM, et al. *Clin Transl Allergy*. 2023;13:e12288.

Study Design (NCT05259917)

KONFIDENT: International, Randomized, Double-blind, Placebo-controlled Phase 3 Trial

STUDY POPULATION:

- Confirmed diagnosis of HAE-C1INH
- Age ≥12 years
- ≥2 attacks within 3 months
- Stable LTP

R[a]

Attack 1 Treatment	Attack 2 Treatment	Attack 3 Treatment
Sebetralstat 1-2 doses of 300 mg	Sebetralstat 1-2 doses of 600 mg	Placebo 1-2 doses
Sebetralstat 1-2 doses of 300 mg	Placebo 1-2 doses	Sebetralstat 1-2 doses of 600 mg
Sebetralstat 1-2 doses of 600 mg	Sebetralstat 1-2 doses of 300 mg	Placebo 1-2 doses
Sebetralstat 1-2 doses of 600 mg	Placebo 1-2 doses	Sebetralstat 1-2 doses of 300 mg
Placebo 1-2 doses	Sebetralstat 1-2 doses of 300 mg	Sebetralstat 1-2 doses of 600 mg
Placebo 1-2 doses	Sebetralstat 1-2 doses of 600 mg	Sebetralstat 1-2 doses of 300 mg

All attack locations and severity eligible (except for severe laryngeal attacks)

PRIMARY ENDPOINT:

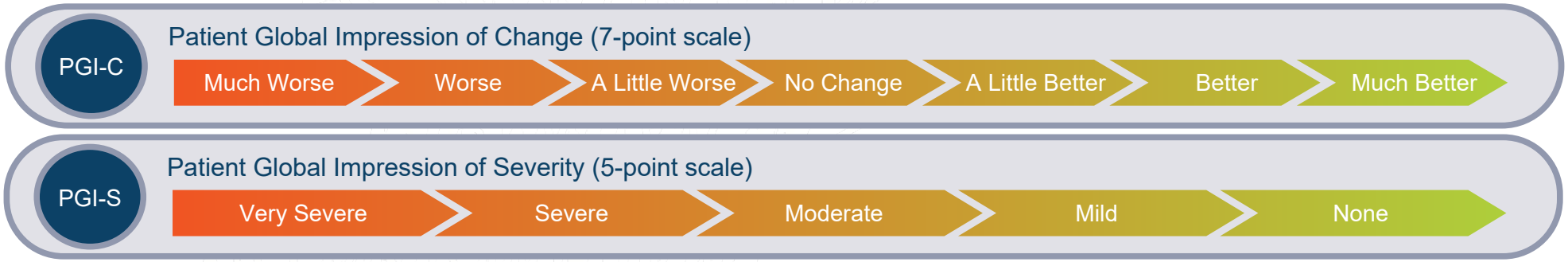
- **Time to beginning of symptom relief**
  (PGI-C rating of at least 'A Little Better' for ≥2 time points in a row within 12 hours)

KEY SECONDARY ENDPOINTS:

- **Time to reduction in attack severity**
  (decrease in PGI-S rating for ≥2 time points in a row within 12 hours)
- **Time to complete attack resolution**
  (PGI-S rating of "None" within 24 hours)

[a]1:1:1:1:1:1 randomization stratified by treatment at enrollment (conventional on-demand therapy only versus stable LTP).
LTP, long-term prophylaxis; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; R, randomization.

Patient Global Impression Scales



Participants

	Participants with at least 1 attack (N=110)
Median age, years (IQR)	39.5 (25.0 to 49.0)
Female sex, n (%)	66 (60.0)
Median BMI, kg/m²	26.2 (22.8 to 31.7)
Race, n (%)	
White	92 (83.6)
Asian	10 (9.1)
Black or African American	1 (0.9)
Other or Not reported	7 (6.3)
HAE-C1INH type, n (%)	
Type 1	101 (91.8)
Type 2	9 (8.2)
Median time since diagnosis, years (IQR)	12 (7 to 22)
Current treatment regimen, n (%)	
On-demand only	86 (78.2)
On-demand + LTP	24 (21.8)

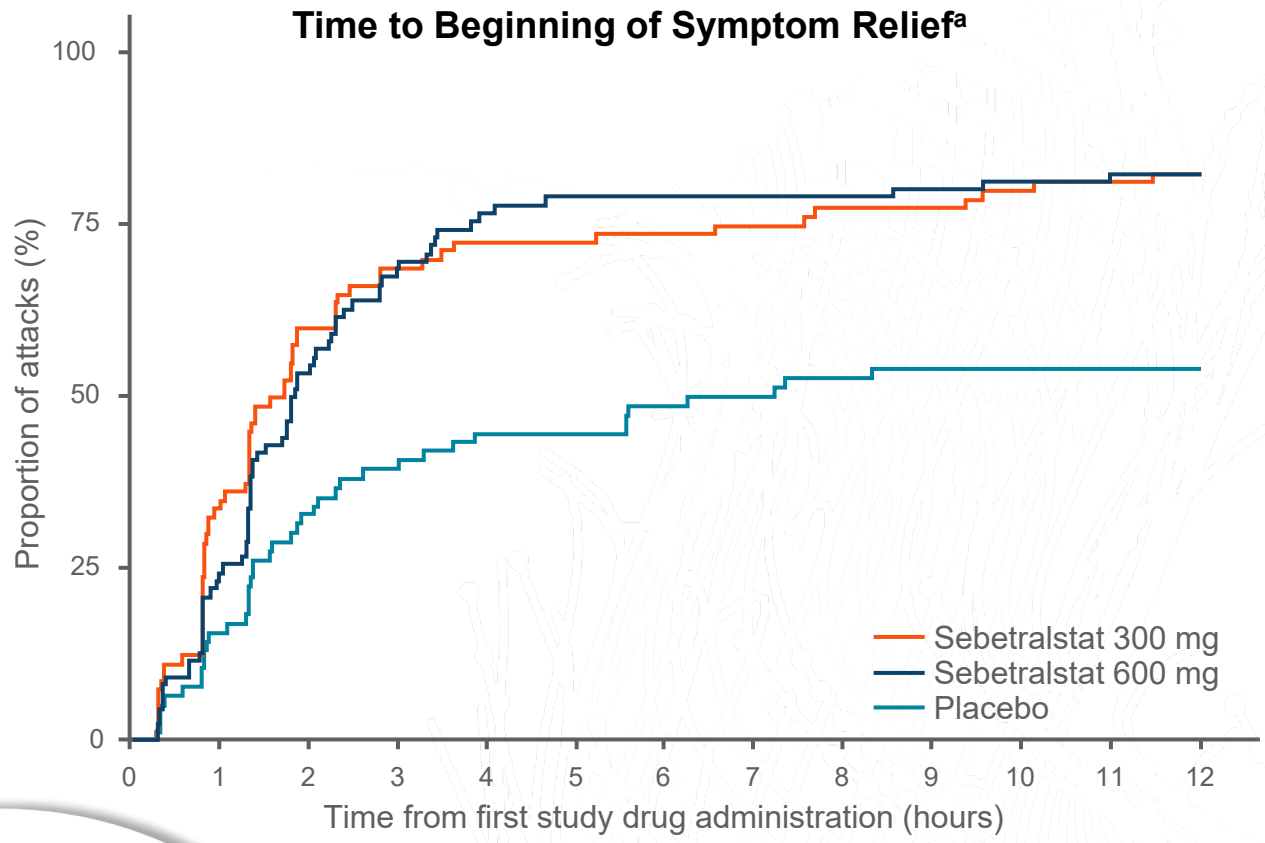
BMI, body mass index; IQR, interquartile range.

Attack Characteristics

	Sebetralstat 300 mg (n=87)	Sebetralstat 600 mg (n=93)	Placebo (n=84)	All Attacks (N=264)
Baseline pooled attack locations, n (%)[a]				
Mucosal (abdomen, larynx/throat[b])	36 (41.4)	44 (47.3)	40 (47.6)	120 (45.5)
Subcutaneous (all others)	49 (56.3)	49 (52.7)	44 (52.4)	142 (53.8)
Baseline PGI-S category, n (%)[a,c]				
Mild	36 (41.4)	41 (44.1)	36 (42.9)	113 (42.8)
Moderate	35 (40.2)	34 (36.6)	33 (39.3)	102 (38.6)
Severe/Very severe	14 (16.1)	18 (19.4)	13 (15.5)	45 (17.0)
Median time from onset of attack to first administration, minutes (IQR)	35 (6 to 130)	41 (5 to 142)	51 (6 to 166)	41 (6 to 140)
Attacks treated in <60 minutes, n (%)	53 (60.9)	50 (53.8)	44 (52.4)	147 (55.7)

[a]Baseline PGI-S score and baseline attack location is missing for two attacks in the sebetralstat 300 mg group.
[b]Among mucosal attacks, 8 attacks involved the larynx: 2 attacks in the sebetralstat 300 mg group, 2 attacks in the sebetralstat 600 mg group, and 4 attacks in the placebo group.
[c]Baseline PGI-S score was "None" for 2 attacks in the placebo group.

Primary Endpoint: Time to Beginning of Symptom Relief



	Sebetralstat 300 mg (n=87)	Sebetralstat 600 mg (n=93)	Placebo (n=84)
***P* value[b]**	**<0.0001**	**0.0013**	**–**
Median	1.61 h	1.79 h	6.72 h
IQR	0.78 to 7.04	1.02 to 3.79	1.34 to >12

[a]Defined as a rating of at least "A Little Better" on the PGI-C scale for at least 2 time points in a row. [b]Adjusted *P* value compared with placebo.

Median Time to Beginning of Symptom Relief by Attack and Participant Characteristics

Median (IQR)	Sebetralstat 300 mg ●	Sebetralstat 600 mg ▲
All attacks	**1.61 (0.78 to 7.04)**	**1.79 (1.02 to 3.79)**
By baseline severity[a]		
None/Mild (●n=36; ▲n=41)	1.70 (0.78 to 3.47)	1.82 (1.08 to 3.97)
Moderate (●n=35; ▲n=34)	1.56 (0.78 to 7.95)	2.11 (1.30 to 5.94)
Severe/very severe (●n=14; ▲n=18)	1.41 (0.79 to 2.78)	1.51 (0.79 to 2.98)
By pooled attack location[a]		
Mucosal (●n=36; ▲n=44)	1.29 (0.77 to >12)	1.32 (0.79 to 2.78)
Subcutaneous (●n=49; ▲n=49)	1.65 (0.98 to 2.78)	2.12 (1.30 to 9.04)

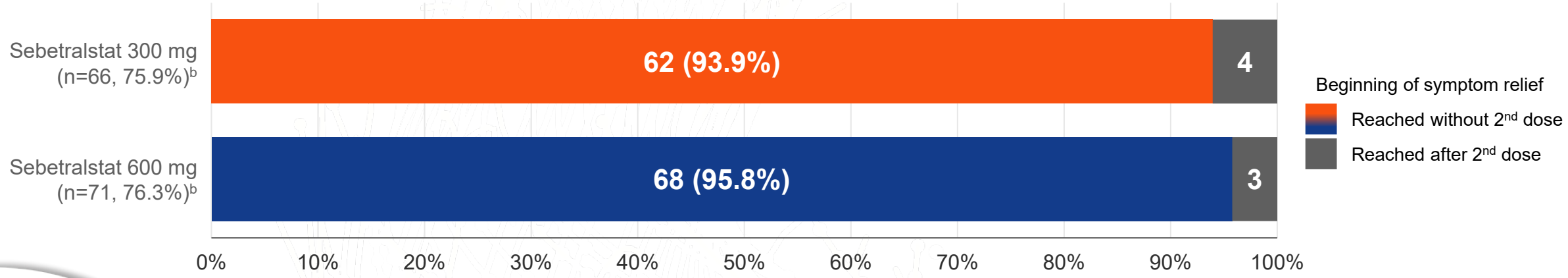
Median (IQR)	Sebetralstat 300 mg ●	Sebetralstat 600 mg ▲
All attacks	**1.61 (0.78 to 7.04)**	**1.79 (1.02 to 3.79)**
By treatment paradigm		
On-demand only (●n=68; ▲n=72)	1.35 (0.78 to 6.54)	1.77 (1.02 to 3.79)
On-demand + LTP (●n=19; ▲n=21)	1.85 (0.79 to 10.12)	2.03 (0.78 to 3.89)
By geography		
Europe (●n=44; ▲n=49)	1.78 (0.98 to 9.36)	1.77 (1.02 to 3.33)
US (●n=27; ▲n=28)	1.28 (0.77 to 3.12)	1.77 (1.31 to 3.89)
Asia/Pacific (●n=16; ▲n=16)	1.70 (0.77 to 2.27)	2.30 (0.86 to 4.34)

[a]PGI-S score and baseline attack location is missing for two attacks in the sebetralstat 300 mg group.

Time to Beginning of Symptom Relief: Number of Administrations

	Sebetralstat 300 mg (n=86)	Sebetralstat 600 mg (n=95)
Number of attacks treated with, n (%)		
1 administration	53 (61.6)	56 (58.9)
2 administrations	33 (38.4)	39 (41.1)
Median time between administrations, h[a]	3.9	3.8

Proportion of attacks reaching beginning of symptom relief without a second administration[a]



[a]Attacks with 2 administrations in which timing of second administration was reported (sebetralstat 300 mg, n=28; sebetralstat 600 mg, n=35; placebo, n=39).
[b]Among attacks reaching beginning of symptom relief within 12 hours.

Key Secondary Endpoints

	Sebetralstat 300 mg (n=87)	Sebetralstat 600 mg (n=93)	Placebo (n=84)
Time to reduction in severity within 12 hours[a,b]			
Adjusted *P* value compared with placebo	0.004	0.003	–
Median (IQR)	9.27 (1.53 to >12)	7.75 (2.19 to >12)	>12 (6.23 to >12)
Time to complete attack resolution within 24 hours[b,c]			
Adjusted *P* value compared with placebo	0.002	<0.001	–
Median (IQR)	>24 (8.58 to >24)	24.00 (7.54 to >24)	>24 (22.78 to >24)
Proportion of attacks reaching complete resolution within 24 hours	42.5%	49.5%	27.4%

[a]Defined as at least a one-level reduction from baseline in PGI-S for at least 2 time points in a row.
[b]Key secondary endpoints were tested in a fixed sequence and were adjusted for multiplicity.
[c]Defined as a PGI-S rating of "None."

Safety

Number of patients with, n (%)	Sebetralstat 300 mg (n=86)	Sebetralstat 600 mg (n=93)	Placebo (n=83)
Any TEAE	17 (19.8)	14 (15.1)	17 (20.5)
Treatment-related TEAE[a]	**2 (2.3)**	**3 (3.2)**	**4 (4.8)**
Serious TEAEs	1 (1.2)[b]	2 (2.2)	0
Treatment-related serious TEAE	**0**	**0**	**0**
Severe TEAEs	1 (1.2)[b]	0	0
Treatment-related severe TEAE	**0**	**0**	**0**
Any TEAE leading to permanent discontinuation	0	0	0
Any TEAEs leading to death	0	0	0

The observed safety profile of sebetralstat was no different from placebo

[a]Treatment-related TEAEs were 1 event each of dyspepsia and fatigue with 300 mg, 1 event each of dyspepsia, nausea, headache, and hot flush with 600 mg, and 1 event each of nausea, headache, dysgeusia, menstruation irregular, and rash with placebo.
[b]The severe TEAE and serious TEAE listed are the same event: lumbar disc herniation that required hospitalization and was deemed severe by the investigator.
TEAE, treatment-emergent adverse event.

Key Takeaways

- An oral on-demand treatment option is desirable to improve **compliance with treatment guidelines** and **diminish adverse drug reactions**
- **Sebetralstat,** an oral plasma kallikrein inhibitor, **enabled early treatment of attacks**
- Compared to placebo, attacks treated with sebetralstat demonstrated **faster times to beginning of symptom relief, severity reduction, and complete attack resolution**, and was consistent across clinically relevant subgroups
- The observed **safety profile of sebetralstat was no different from placebo**
- Long-term safety and efficacy is being studied in the KONFIDENT-S 2-year OLE trial (Poster #L-TPS03)

Simultaneous with this publication, the results from KONFIDENT are now published in the *New England Journal of Medicine*:

Riedl M et al. *N Eng J Med*. 2024. doi:XXXX.

QR code

OLE, open-label extension. KONFIDENT-S: Clinicaltrials.gov, NCT0550505916; EudraCT, 2021-001176-42.

KONFIDENT Authors

Marc A. Riedl, MD
Henriette Farkas, MD, PhD, DSc
Emel Aygören-Pürsün, MD
Fotis Psarros, MD
Daniel F. Soteres, MD
Maria Staevska, MD
Mauro Cancian, MD
David Hagin, MD, PhD
Daisuke Honda, MD, PhD
Isaac Melamed, MD
Sinisa Savic, PhD
Marcin Stobiecki, MD
Paula J. Busse, MD
Eunice Dias de Castro, MD, PhD
Nancy Agmon-Levin, MD
Richard Gower, MD
Aharon Kessel, MD
Marcin Kurowski, MD
Ramon Lleonart, MD
Vesna Grivcheva Panovska, MD
H. James Wedner, MD
Paul K. Audhya, MD
James Hao, PhD
Matthew Iverson, MPH
Michael D. Smith, PharmD
Christopher M. Yea, PhD
William R. Lumry, MD
Andrea Zanichelli, MD
Jonathan A. Bernstein, MD
Marcus Maurer, MD
Danny M. Cohn, MD

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