

The Voice of the Patient

A series of reports from the U.S. Food and Drug Administration's (FDA's)
Patient-Focused Drug Development Initiative

Systemic Sclerosis

Public Meeting: October 13, 2020

Report Date: June 30, 2021

Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration (FDA)

Table of Contents

Introduction 3

- Overview of Systemic Sclerosis 3
- Meeting Overview..... 3
- Report Overview and Key Themes..... 5

Topic 1: Disease Symptoms and Daily Impacts That Matter Most to Patients 6

- Perspectives on Most Significant Symptoms 6
- Overall Impact of Systemic Sclerosis on Daily Life 9

Topic 2: Patient Perspectives on Treatments for Systemic Sclerosis..... 11

- Perspectives on Current Treatments 11
- Perspectives on Ideal Treatments for Systemic Sclerosis 13

Summary of Comments Submitted to the Public Docket 14

Conclusion..... 16

Appendix 1: Meeting Agenda 17

Appendix 2: Patient and FDA Panel Participants..... 20

Appendix 3: Meeting Polling and Scenario Questions..... 21

Introduction

On October 13, 2020, FDA held a public meeting to hear perspectives from patients with systemic sclerosis, caregivers, and other patient representatives regarding the symptoms of systemic sclerosis that matter most to patients and current approaches to treating this disease. In 2012, FDA established the Patient-Focused Drug Development (PFDD) initiative to more systematically obtain the patient perspective on specific diseases and their currently available treatments. The systemic sclerosis public meeting was the Agency's 29th Patient-Focused Drug Development meeting.

More information about Patient-Focused Drug Development can be found at <https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development>.

Overview of Systemic Sclerosis

Systemic sclerosis, also known as systemic scleroderma, is an autoimmune disorder that affects the skin and internal organs. Systemic sclerosis is characterized by fibrosis, referring to the excess production of collagen, a structural protein that normally strengthens and supports connective tissues throughout the body. The symptoms of systemic sclerosis can vary greatly from person to person, ranging from very mild to life-threatening. They usually begin with episodes of Raynaud's phenomenon, which entails feelings of numbness and cold in the fingers, toes, and other extremities in response to cold temperatures or stress. Another symptom of systemic sclerosis is calcinosis, the buildup of calcium deposits in the skin and subcutaneous tissues.¹ Other symptoms of systemic sclerosis can include decline in organ function, such as the lungs and gastrointestinal tract. In the United States, approximately 75,000 to 100,000 individuals have systemic sclerosis. The exact causes of systemic sclerosis are unknown. Systemic sclerosis tends to occur in two different subtypes: diffuse and limited. Diffuse systemic sclerosis is characterized by skin hardening and problems in many organs of the body. Limited systemic sclerosis usually consists of calcinosis, Raynaud's phenomenon, esophageal motility dysfunction, sclerodactyly, and telangiectasia. Most systemic types of sclerosis are typically diagnosed between ages 30 and 50.²

There is no cure and there are no FDA-approved treatments for systemic sclerosis. However, there are two FDA-approved treatments to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD). There are also several treatments used off-label to manage systemic sclerosis, including nonsteroidal, anti-inflammatory medications or corticosteroids (for pain relief) and immunosuppressive medications (to alleviate skin thickening and damage to internal organs). Other common therapies include skin lotions and moisturizers for skin itch, and physical therapy and exercise to maintain muscle strength.³

Meeting Overview

This virtual (online only) meeting provided FDA the opportunity to hear directly from patients, caregivers, and other patient representatives about their experiences with systemic sclerosis and its

¹ <https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Scleroderma>

² <https://ghr.nlm.nih.gov/condition/systemic-scleroderma>

³ <https://www.hopkinsscleroderma.org/patients/scleroderma-treatment-options/>

treatments. Patients, caregivers, and other patient representatives were encouraged to participate in the facilitated discussion by submitting comments online or by phone. The discussion focused on two key topics: (1) health effects and daily impacts of systemic sclerosis and (2) patients' perspectives on current approaches to treating systemic sclerosis.

Each topic began with comments shared from a panel of patients and caregivers (Appendix 2), followed by large group facilitated discussions inviting other patients, caregivers, and patient representatives to call in and submit written comments through the webcast platform. An FDA facilitator led the discussions, and a panel of FDA clinical review staff (Appendix 2) asked follow-up questions. Patients and caregivers were periodically invited to respond to polling questions (Appendix 3), which provided a sense of the demographic makeup and how many participants shared a particular perspective.

Approximately 250 people attended the virtual meeting through the live webcast, with around 80 identifying themselves as patients with systemic sclerosis or patient representatives. Participants ranged from 18 to over 71 years of age, with roughly half of participants over 51. Almost 75 percent of participants were female. Participants represented a range of experiences with systemic sclerosis, with approximately 75% of respondents indicating they had experienced skin tightening and some level of organ damage. Some respondents reported comorbid features of another systemic rheumatic disease such as systemic lupus erythematosus (SLE), rheumatoid arthritis, polymyositis, or Sjögren's syndrome. Although participants in this meeting may not fully represent the diverse population living with systemic sclerosis, the perspectives they shared reflected a diverse set of experiences with the symptoms and treatments for this disease.

To supplement the input gathered at the meeting, individuals with systemic sclerosis and others were encouraged to submit comments to a public docket,⁴ which was open until December 15, 2020. In total, 13 comments were submitted to the public docket, the majority by individual patients and caregivers.

More information, including the archived webcast and meeting transcript, is available on the meeting website: <https://www.fda.gov/industry/prescription-drug-user-fee-amendments/fda-led-patient-focused-drug-development-pfdd-public-meetings#sclerosis>.

⁴ A *docket* is a repository through which the public can submit electronic and written comments on specific topics to U.S. federal agencies such as FDA. More information can be found at www.regulations.gov.

Report Overview and Key Themes

This report summarizes the input shared by patients and patient representatives during the meeting. It also includes a summary of the comments submitted to the public docket. To the extent possible, the terms used in this report to describe systemic sclerosis symptoms, impacts, and treatment experiences reflect the words used by the patients, caregivers, and commenters to the docket. It is possible that the views and experiences shared in this report may not fully capture the range of experiences represented among the broader population of patients with systemic sclerosis.

The input from the meeting and docket comments describe in rich detail the impact of systemic sclerosis on patients. Participants highlighted the physical, emotional, and social toll systemic sclerosis takes on daily life, emphasizing the need for new treatment options. Several key themes emerged from this meeting:

- Participants emphasized the range of symptoms they experience from systemic sclerosis. They described systemic sclerosis as a debilitating disease that causes physical discomfort and affects almost every aspect of daily living.
- Participants stressed the physical impact that systemic sclerosis has on their lives. They described daily difficulties from gastrointestinal (GI) symptoms, contractures of the hands, and Raynaud's, which complicate efforts to perform daily activities, such as getting ready in the morning, buttoning shirts, eating and swallowing, and participating in physical activities such as dancing and painting. They described the trauma of the loss of digits, pain, and calcinosis, contributing to anxiety and depression. They discussed the impact of systemic sclerosis on working and attending school, maintaining personal relationships, and on family members and family life.
- Participants shared their experiences with the use of prescription and non-prescription medicines. The prescription and non-prescription medicines varied in and their various routes of administration (topical, oral, and intravenous). Participants highlighted the varying degrees of success in managing their symptoms with these therapies. Many described variability in medicine effectiveness and stressed the need for improved treatment options. Others highlighted the importance of adequate access to available treatments and expressed concern about potential long-term effects of available treatments. The discussion also highlighted the unmet medical need for more and better treatments for long-term management of GI symptoms caused by systemic sclerosis.

The patient input generated through this Patient-Focused Drug Development meeting and the public docket comments strengthens FDA's understanding of the daily burden of systemic sclerosis and patient perspectives on the treatments currently used to treat systemic sclerosis. FDA staff will carefully consider this input during the drug development process, when advising sponsors on their drug development programs, and when assessing products for market approval.

This input may help drug developers understand how to develop better endpoints for clinical trials to measure those aspects of systemic sclerosis that are important to patients. It may help drug developers select or develop questionnaires that measure important concepts and engage with the FDA as they develop treatments. The information from these meetings can also help support the FDA review of

clinical trial questionnaires to confirm that they are adequately capturing patient and caregiver perspectives on health outcomes.

Topic 1: Disease Symptoms and Daily Impacts That Matter Most to Patients

The first discussion topic focused on patients' experiences with systemic sclerosis and its impact on their daily lives. FDA was particularly interested in hearing participants describe specific symptoms and impacts in their own words. FDA was also interested in learning about how systemic sclerosis affects their ability to live normally and perform activities as fully as they would like.

Five panelists (Appendix 2) provided comments to start the dialogue. Panelists included:

- A 38-year-old woman with systemic sclerosis. She was diagnosed at age 19 and experienced sudden and rapid progression of symptoms such as Raynaud's phenomenon, digital ulcers, contractures in her hands, and organ damage. Her symptoms continue to progress steadily.
- A 55-year-old woman who has had trouble receiving a diagnosis for her symptoms. She has experienced chronic fatigue, pain, and difficulty breathing.
- A woman who has been living with systemic sclerosis for 35 years. She has experienced Raynaud's phenomenon, skin tightening, calcinosis, and temperature sensitivity. The temperature sensitivity has interfered with her ability to sleep, requiring her to wear layers and use several comforters to sleep.
- A 57-year-old woman who was diagnosed with systemic sclerosis 22 years ago. She initially experienced pain in her hands and joints which has progressed to skin tightening that limits mobility. She describes the calcinosis as the most impactful of her symptoms.
- A woman who was diagnosed with systemic sclerosis at age 29 and has experienced chronic pain for the last 24 years of her life. She experienced pain and lung damage during the nine years before she was diagnosed and is now in need of supplemental oxygen.

The panelists' statements provided a vivid depiction of the discomfort and burden of systemic sclerosis on many aspects of daily life. They described the physical symptoms and discomfort they experienced and the impacts of systemic sclerosis on their daily lives. Based on the perspectives that participants shared via phone call and web comments during the facilitated large group discussion, the panelist comments reflected the experiences of participants on the webcast.

Perspectives on Most Significant Symptoms

Participants described a range of experiences with systemic sclerosis. In polling questions (Appendix 3, Q7), participants were asked to identify which symptoms of their systemic sclerosis had the most significant impact on their daily life. The top three significant symptoms of systemic sclerosis, based on the number of responses received, were 1) painful cold sensitivity in hands and/or feet (Raynaud's phenomenon), 2) digestive symptoms, and 3) fatigue. Many described changes in their systemic sclerosis over time, experiencing rapid onset of symptoms that continued to worsen over time. Others had a

more gradual progression of symptoms. Some felt their systemic sclerosis was well managed, and they only experienced intermittent flare-ups. The facilitated large group discussion provided insight into how these symptoms of systemic sclerosis affect patients. The range of symptoms discussed with participants are described further below.

Painful cold sensitivity (Raynaud's phenomenon)

Almost all participants identified painful cold sensitivity and numbness in the hands and/or feet (Raynaud's phenomenon) as one of the most significant symptoms of their systemic sclerosis. Several described intolerance to cold temperatures, exposure to which would exacerbate Raynaud's symptoms. One participant shared that she sleeps with two comforters and a heavy blanket despite warm temperatures. Another described Raynaud's as being much more crippling than it sounds and one said her Raynaud's visibly manifested by her hands turning colors. Some stated that their Raynaud's is triggered by stress, anger, cold, heat, air conditioning, and "all types of stressors." Many participants shared that their systemic sclerosis symptoms started with Raynaud's phenomenon and then progressed to other symptoms. One stated she had "started to lose part of one finger" due to Raynaud's. Others stated that their Raynaud's caused weakness, joint stiffness, and pain.

Skin symptoms

Many participants identified skin symptoms as one of the significant physical burdens associated with their systemic sclerosis. Skin tightness and stiffness was frequently described. Participants referenced skin tightness and stiffness that occurred in parts of the body including mouth, arms, elbows, hands, fingers, wrists, and feet. One participant described skin tightness over her entire body, making her "arms, hands, stomach, and legs hard like a rock." Another described her skin as being "taut, discolored, itchy, and shiny." A few shared the experience of difficult and stressful dental visits. For example, one participant with skin tightness said about her dental appointment, "I thought that my mouth was going to rip apart, because it's much smaller than it used to be." A few participants stated the stiffness in their skin made it difficult to bend, reach things, stretch, and kneel. One expressed sadness that she no longer looks the way she did 20 or 30 years ago, sharing, "My lips are thin, my nose is pointy, and my face is so different that high school classmates, friends, and relatives I do not see very often do not recognize me."

Contractures

Many participants talked about contractures in their hands, severely impairing their ability to use their hands. Several described curved fingers and curved hands that cannot be straightened, undermining their dexterity. One participant explained how she could not bend her thumb at all. Another said, "My fingers are crooked, and I cannot make a fist since some of the joints are too stiff and skin is too tight. My fingernails look like a witch's fingers and curl around the top of my finger or do not exist anymore." Many participants described how contractures in their hands limited their ability to do things such as button shirts, put on jewelry, comb their hair, and type.

Calcinosis and digital ulcers

Many participants described their experience with calcinosis and ulcers on their digits, hands, and other parts of their body. One participant described her experience with calcinosis as being like "a little rock coming out of your fingers. If you accidentally touch it or hit it on anything, the pain just sends you through the roof." Another described calcinosis in her big toe that prevented her from putting her shoes on and walking: "[her] big toe got really swollen and red and hot." One participant described calcinosis

as a “thick white toothpaste” that feels as if she had hit her finger with a hammer. Some participants had surgery on the affected areas to remove the calcinosis, but indicated they are not likely to undergo the surgery again due to the pain and complications following the surgery. One participant shared that the calcinosis in her fingertips “makes it extremely difficult to use [her] hands since any pressure put on the finger causes nerve pain.” Another stated the sores caused by calcinosis take years to heal.

Many participants commented on the agony of digital ulcers occurring with calcinosis. One shared that the ulceration and infection of a finger that would not heal resulted in its amputation. Another described digital ulcers as “absolute agony if they get knocked, especially if I also have calcinosis.” A different participant expressed that digital ulcers frequently “take forever to heal and have caused permanent damage/pitting/scar tissue.” One participant described digital ulcers as a “pain that is indescribable. It is almost like a nerve pain as well as if you got a little blow of air on it, it is excruciating.”

Gastrointestinal (GI) symptoms

Almost all participants mentioned GI symptoms as having a significant impact on their lives. Many expressed that they have difficulty swallowing and experience frequent acid reflux. One participant stated that difficulty swallowing made her “have to drink after every bite of food.” Another described her experience with acid reflux and shared that she vomits very easily, even when she does not feel nauseous. Several participants shared that they sleep propped up or on a wedge pillow to decrease the reflux. Many of the same individuals shared that they also experience frequent vomiting, nausea, bloating, diarrhea, constipation, and impaired motility and absorption. One shared how bladder and bowel incontinence dramatically affects quality of life “and confines [her at] home a lot of days.” One participant avoids eating lunch at work because “eating might make me vomit or set off more diarrhea.” Another reflected on how her diarrhea is so severe that it can be debilitating.

Chronic fatigue

Almost all participants highlighted that they struggle with chronic fatigue as a symptom of their systemic sclerosis. One participant reflected on being tired all the time, even after taking a nap. Another emphasized the link between her constant exhaustion and chronic depression, stating, “I mostly want to sleep so my mind shuts down and I don’t have to deal with the realities of systemic sclerosis.” Another participant described bad days, when she remains bedridden, in “a hibernation type of deep sleep.” A few participants talked about often feeling dizzy when fatigued. One said she cannot stand without holding onto a chair or wall. One participant talked about uncontrollable spikes in fatigue that come unexpectedly. Another stated that her whole body can be drained, “even just going to get something to eat from the kitchen.”

Several participants highlighted the differences between chronic fatigue and brain fog. Many shared that they experienced both fatigue and brain fog. One participant shared how brain fog causes difficulty thinking and putting concepts together, which can be challenging in a work environment. Another emphasized that when she has brain fog, she cannot talk, find words, nor think clearly.

Chronic pain

Many participants described the experience of daily pain. To describe the pain in her hands, one participant said, “It’s as if all the skin that was on my hands to cushion the bones is no longer there and it’s like you’re hitting your raw bone on something accidentally.” Some participants shared how their pain keeps them from sleeping at night. One described a bad day as “me in my PJ’s all day with my cats,

watching TV because it literally hurts to breathe, let alone get out of bed.” Another referenced the impact pain has on her emotions, suffering mood changes and irritability toward people, even though such feelings run counter to her personality.

Comorbid conditions & other symptoms

Participants described several comorbid conditions, in addition to the symptoms experienced from systemic sclerosis, including:

Other Symptoms

- Lung involvement, which for many leads to difficulty breathing and can include interstitial lung disease and/or pulmonary fibrosis and pulmonary hypertension.
- Insomnia, which some stated is a result of the constant pain they experience. One participant stated she has “never been able to sleep.”
- Itching, which for some has led to permanent scars and difficulty sleeping.
- Temperature sensitivity, which participants experienced as a common component of Raynaud’s phenomenon.

Comorbid Conditions

- Telangiectasia, which appears as threadlike red lines or patterns on the skin. Some participants experienced this on their face and palms.
- Sjogren’s Syndrome, a condition that is characterized by dry eyes and dry mouth.
- Other comorbid conditions include neuropathy, tachycardia, lupus, fibromyalgia, pulmonary hypertension, hair loss, and itching.

Overall Impact of Systemic Sclerosis on Daily Life

Throughout the meeting, participants described in rich detail the impact that systemic sclerosis has on daily life, including:

- **The ability to perform daily activities.** Most participants who spoke shared that systemic sclerosis made it harder to perform daily activities such as caring for themselves, their family, and doing chores around the house.

Many participants described the challenges they faced with housework. Several noted they could not bend, stretch, or kneel without difficulty. One participant stated, “If I’m having a good day, I will choose to do some housework, knowing that I will need one to three days of recovery.” Another noted, “Any activity involving the use of my hands has become more and more difficult. Opening jars is almost impossible.” Several participants also mentioned difficulty with washing dishes.

Systemic sclerosis made getting ready in the morning increasingly difficult for several participants. One stated that “just putting on jewelry is difficult” due to the contractures in her hands. Another expressed difficulty putting on socks and combing her hair in the mornings. One participant shared that it takes her three to four hours each morning to get dressed and out of the house because of gastrointestinal symptoms. Another participant explained that she is constrained to the house until 11am each morning because of diarrhea.

Many participants talked about the challenges of work and school. Several shared that typing was difficult because of contractures in their hands. Contractures and fatigue left another participant unable to finish nursing school. Another shared that GI symptoms make her late for work every day, in part because she drives a longer route to work in case she needs to stop at the gas station to use the restroom.

- **The ability to participate in physical activities.** Several participants shared that they were forced to give up activities they had enjoyed, such as dancing, swimming, playing the piano, and painting. Others noted difficulty with walking and getting around. One participant said some days she can walk almost half a mile, but on other days she cannot walk at all. Another described deterioration of the cushion in her feet causing difficulty with walking, that “feels like walking on bones.” One participant was no longer able to go upstairs, using a walker and wheelchair to get around. Another participant described her experience with calcinosis in her toe which made it extremely difficult for her to walk. Some required continuous supplemental oxygen when engaging in physical activity. For example, one participant described experiencing shortness of breath due to pulmonary arterial hypertension and requiring oxygen when exercising.
- **The ability to eat.** Almost every participant emphasized that eating difficulties (including heartburn) and dietary restrictions had a major impact on their lives. One participant expressed limiting herself to one meal a day so as to not go to the emergency room for GI symptoms, whereas another shared that she typically must force herself to eat. One participant described herself as a “professional chewer” because she has learned to chew her food very well to make swallowing, digestion, and absorption of her food easier. Others had extreme food allergies which restricted them to a limited diet. One noted that food intolerances, causing constant nausea, aches and pains, low energy, and foggy-brain episodes, restricted her to a diet of only four foods along with 10 hours of total parenteral nutrition at night. Others expressed how the skin on their face was so tight it made it difficult to chew and swallow. One participant stated, “Every meal presents a challenge - accompanied by 2-3 pints of water and sometimes regurgitation.”
- **The ability to access medical care.** Many participants described challenges in accessing medical care, owing to lack of medical understanding and education around systemic sclerosis. One participant shared that she often must go into the emergency room for a minor event, such as getting allergy medicine, because general practitioners have appeared uncomfortable treating her. Frequent changes to treatment regimens had plagued another participant, who found that her doctors often had to experiment to determine which treatments would help her. Several also talked about their difficulty receiving a diagnosis for their condition. It took over a year of frequent visits to a primary care provider before one participant was tested for pulmonary function and diagnosed with systemic sclerosis.
- **Severe emotional impact.** Severe emotional distress—*anxiety and depression*, in particular—was nearly universal among participants. Several worried about the long-term effects of medication, with one noting, “The issue of premature death concerns me the most about systemic sclerosis.” Another shared, “[I fear] not being able to take care of myself and dying young.”

The loss of digits had a severe emotional impact for many participants; one described it as “[a] traumatic event... [that] has caused me to suffer from depression.” The difficulty of getting a proper diagnosis caused emotional distress for some. One participant said, “[The] lack of information when getting diagnosed was difficult, depressing, and scary.” Another found it difficult to discuss her pain, symptoms, and ultimate diagnosis: “I knew that it was very, very real and after a traumatic experience of locking up in my bathtub for a half hour by myself... I finally revealed my truth regarding my pain.” Another participant shared that due to her skin tightening on her face, she feels she has lost part of her identity because friends and relatives sometimes do not recognize her.

Topic 2: Patient Perspectives on Treatments for Systemic Sclerosis

The second discussion topic focused on patients’ experiences with therapies for systemic sclerosis. Five panelists (Appendix 2) provided comments to start the dialogue. Panelists were:

- A 55-year-old woman, diagnosed three years ago, who decided to focus on lifestyle and diet modifications to manage her systemic sclerosis.
- A 67-year-old woman, diagnosed 14 years ago, who has experienced a wide range of prescription drug and nondrug therapies to control her symptoms.
- A 53-year-old woman, diagnosed 10 years ago, who underwent a stem cell transplant in addition to other therapies.
- A woman, diagnosed as a child 45 years ago, who depends on the compounding of all prescription and over-the-counter medications, owing to her intolerance to the binders and fillers used in pharmaceutical manufacturing.
- A woman, diagnosed 20 years ago, also having used a wide range of prescription drug and nondrug therapies.

In the large group facilitated discussion that followed the panelist comments, the larger group of patients and patient representatives discussed experiences with prescription drugs, medical procedures, and non-drug therapies. Overall, participants reported feelings of frustration at the lack of treatment options available for systemic sclerosis. Many faulted existing treatment options for providing short-term control of symptoms, but not effectively slowing or reversing of disease progression. Several emphasized the need for additional treatment options for systemic sclerosis. Participant perspectives on the benefits and downsides of their therapies, as well as what they would look for in an ideal treatment, are summarized below.

Perspectives on Current Treatments

Participants discussed a range of approaches they used to treat their systemic sclerosis. Almost all participants reported (Appendix 3, Q10) use of prescription drugs, such as immunosuppressants, proton pump inhibitors, vasodilators, and topical corticosteroids. Moisturizers, physical therapy and exercise, and diet modifications were also part of their treatment regimen. One participant highlighted her experience as a recipient of a stem cell transplant.

Prescription and nonprescription medication

Participants reported using several prescription and nonprescription drug treatment options, including:

- **Immunosuppressants** - Immunosuppressants were the most commonly used type of prescription medication, although they often were reported to be ineffective, with significant downsides. Some participants reported continued progression of their systemic sclerosis, despite taking the medication. Others noted “little progress in any meaningful cure or reversal of damage.” One participant stopped use of immunosuppressant and chemotherapy drugs because she had many precancerous/cancerous cells on her health exams. However, a few shared that immunosuppressants helped treat the symptoms of their interstitial lung disease.
- **Proton pump inhibitors** - Many participants had used proton pump inhibitors, but a few felt these products were ineffective, particularly in treating chronic or ongoing GI symptoms. One participant cannot leave the house some days without her anti-diarrheal medication. Several others expressed concern about the long-term and high dose use of proton pump inhibitors.
- **Vasodilators** - Several participants used vasodilators and antihypertensive drugs, typically to treat pulmonary hypertension and Raynaud’s phenomenon. For some, vasodilators were the only medications that alleviated symptoms of Raynaud’s phenomenon.
- **Other medications** – Other medications included antidepressants, painkillers, levothyroxine, and rituximab.

Regarding downsides, many participants indicated that their current treatment options temporarily alleviate their symptoms, but also noted that none slowed the progression of systemic sclerosis. Several shared that they try not to take prescription narcotics very often owing to side effects (such as sleep disruption and itching) but noted that enduring the side effects is sometimes “better than being in pain.” One described the inconvenience of her cumbersome regimen as a downside of treatment. Several participants worried about the long-term side effects of their medications such as risk of cancer.

Perspectives on non-drug therapies

In response to a polling question (Appendix 3, Q11), many participants indicated they manage their systemic sclerosis with non-drug therapies, mentioning psychotherapy and emotional support from friends and family. One participant expressed that “If you have a good support system, and you have people who are willing to help you, and you have that positive drive just to get through each day, you can find ways that you never would have thought of to make things happen.” One participant shared the importance of being able to connect with other individuals dealing with the emotional challenges of systemic sclerosis, stating “I need someone to tell me that they have incontinence. When I pooped myself at 40 looking for my child's first bathing suit for his swim meet, which I'm still going to do, I want to know that there's someone else out there [who has gone through this].”

Almost all participants also indicated they practiced yoga, engaged in physical therapy, or exercised regularly. One participant, who exercises regularly to reduce joint pain, said, “By the time I am done, I feel good, with more energy, which is precious when you have an autoimmune condition.” Several participants shared that diet modifications help alleviate some of the GI symptoms and increase their

energy levels. One relied nightly on total parenteral nutrition for 10 hours to receive 70% of her nutrients. To stay independent, many participants highlighted the utility of equipment or tools, such as a shower chair, adjustable mattress, electric scooter, grippers, and door-openers. Others shared that they always have handwarmers or gloves available in case of Raynaud's symptoms.

Perspectives on Ideal Treatments for Systemic Sclerosis

Given the current lack of effective treatment, participants provided a range of perspectives on attributes that they would like to see in an ideal treatment that would slow or halt the progression of systemic sclerosis and improve the quality of patients' lives. Multiple participants expressed the willingness to take greater risk and "accept some side effects" from a hypothetical treatment that would provide "control of disease progression, [an] increase in overall quality of life, and organ preservation."

Several participants expressed a desire for treatments to alleviate specific symptoms of systemic sclerosis, such as digital ulcers, calcinosis, pain, and GI symptoms. One participant expressed that she was willing to risk a lot for relief of digital ulcers because she does not wish to lose any more fingers due to amputations. Another emphasized the need for medications that treat the intestinal tract and address lack of absorption. Some participants wanted treatments with reduced risks (such as cancer risks), relative to current treatments. One said, "In the long term, aggressive treatments that work well and have the potential to damage our organs are not prolonging life or improving on quality of life. They are causing more hardship."

Several participants talked about clinical trial participation considerations. Many commented on their preference for a treatment that could be self-administered from home. Almost all participants described the importance of convenience and ease of administration, preferring not to have to make frequent doctor's appointments for treatment. One also mentioned the relationship between dosing regimen and treatment effectiveness: "Is it multiple times a day? Is it once a day? Because that does impact compliance and ability to really be successful." Some participants also shared that they had difficulty with IVs and lab draws. One said, "Nobody could get the IVs in my arms because the skin was so tight." Another noted, "Many of us with scleroderma have very bad veins, and IVs are pretty traumatic for us."

To help guide the discussion, participants were asked to imagine a hypothetical scenario in which a new self-injectable medication indicated to treat systemic sclerosis had recently been approved by FDA (see full text in Appendix 3). In the clinical trials that were conducted, when injected once weekly the hypothetical medication was shown to reduce the symptom that most significantly impacts the individual's daily life. More common side effects of this therapy may include headache, diarrhea, nausea, stomach or abdominal pain, and weight loss. Rarer but more serious side effects may include infection, seizures, trouble breathing, fever, general feeling of discomfort or illness, and risk of bleeding.

Participants were asked to comment on the first thoughts that came to mind as they heard this scenario. Almost all participants indicated, despite the side effects, they would be interested in the hypothetical treatment. Participants discussed how the convenience of a treatment that could be self-administered easily at home once a week or once a month, without the burden of frequent doctor's appointments was appealing. Participants also mentioned that an oral medication would be preferable to an injectable medication because they have trouble with injections and blood draws. Several also liked the idea of a medication that they could discontinue easily if they found the side effects intolerable.

Summary of Comments Submitted to the Public Docket

Thirteen comments were submitted to the public docket that supplemented the Patient-Focused Drug Development public meeting for systemic sclerosis. Most comments were submitted by patients and caregivers; others came from health care providers, professional organizations, patient groups, and expert researchers. Overall, the experiences and perspectives reflected in the comments received to the docket were similar to those shared during the public meeting via live webcast.

Submitted Comments on Symptoms of Systemic Sclerosis

Comments submitted to the public docket emphasized the physical, emotional, and economic impact of systemic sclerosis. Docket commenters identified all the symptoms of systemic sclerosis that were discussed during the public meeting as well as the additional symptom of tooth resorption. Docket commenters provided many insightful descriptions of the specific ways in which their symptoms manifest. A few select examples are presented below:

- **Painful cold sensitivity (Raynaud’s phenomenon).** Commenters discussed experiences with Raynaud’s phenomenon occurring in their fingers, hands, and other extremities. One commenter shared that her Raynaud’s was usually triggered by cold temperatures, for example from “air conditioning or the freezer section of the supermarket,” as well as “stress and high emotions such as laughing, crying, and experiencing anger.” Another commenter expressed that her “body feels ice cold.” Others shared that they could not tolerate exposure to cold temperatures, experiencing severe pain in their hands and feet.
- **Calcinosis and digital ulcers.** Commenters detailed the severe pain and discomfort associated with calcinosis. Several commenters mentioned how, because of their calcinosis, it can take many weeks, months, or even years for the digital ulcers to heal.
- **GI symptoms.** Many commenters talked about the “constant battle” with GI symptoms. One commenter reported, “I get acid reflux from bending over right after I eat something. I vomit very easily, even when I don’t feel nauseous. I sleep with a wedge pillow to elevate my head and keep acid down.” Another commenter added that “constipation and diarrhea” are a part of “daily life.”

Submitted Comments on the Overall Impact of Systemic Sclerosis on Daily Life

The docket comments reflected the input received during the meeting related to the debilitating impact of systemic sclerosis on the daily lives of patients and their families.

- **The ability to perform daily activities.** Many commenters described the impact of their systemic sclerosis on their ability to perform daily activities. For example:
 - “I was 54 years old (25 years after diagnosis) and I had difficulties getting through a meeting without coughing, being short of breath and hard to talk. I was miserable. I was a Sr. Data Architect at a large PBM and after 35 years of a career in Computers and Data, my lungs would not allow me to continue working. The fatigue at this time really kicked in and I was struggling to get up, ready for work and get to my office by 9am when I got up at 6am.”

- “I had to quit my job because I could no longer manage all of my symptoms and be present at work 8 hours a day.”
 - “This disease has had a significant impact on her [my sister’s] ability to chew and swallow. The symptoms of Raynaud’s and its effects on her hands and feet make commonplace activities difficult and painful. Some elements of her daily life are simply left undone because of the strength and energy they require.”
 - “My mother fought the digital ulcers for many years. They finally removed a finger after it wouldn’t heal and got infected. She constantly battled gastro issues. She was sent home from work several times due to vomiting as the company couldn’t understand it was nothing contagious. She was hospitalized several times for bowel blockages. Her fingers curled and at the end she was wearing very loose t-shirts and sweats as she could no longer manipulate buttons, zippers or any other fasteners.”
- **The ability to participate in physical activities.** Commenters described difficulty participating in physical activities. One commenter noted her impaired ability to walk due to her systemic sclerosis symptoms. She used to walk 1.5 to 2 miles in about 30 minutes, but now she carries supplemental oxygen and can only walk 0.6 miles in 20 minutes. Other commenters noted difficulty going upstairs or limitations walking beyond very brief distances; walkers and wheelchairs were mentioned for longer distances.
 - **Severe emotional impact.** Several commenters emphasized the severe emotional impact of their systemic sclerosis. One wrote about the sense of partial loss of identity, noting that the skin tightening of her face has changed her appearance and caused friends and relatives to not recognize her. Some wrote about difficulty getting diagnosed, and one expressed the emotional impact of “being made out to be a hypochondriac by multiple doctors, nurses, and staff.” Another commenter added that systemic sclerosis “takes people’s lives both mentally and physically.”

Submitted Comments on Current Treatments for Systemic Sclerosis

Docket commenters made statements similar to those expressed by participants of the public meeting. There was a high degree of frustration with the ineffectiveness of available treatments, especially given the cost and side effects. One commenter noted, “There is no medicine or treatment that exists that allows a patient with gastro involvement to live a normal, sustainable life.” Another commenter noted her experience seeking treatment options, saying, “I was evaluated at Duke for a double lung transplant and was rejected because all of my scleroderma issues made it too risky for me to survive recovering from the surgery.”

- **Immunosuppressants.** Several commenters discussed the use of immunosuppressants to slow the progression of lung fibrosis and interstitial lung disease. They noted that, although the immunosuppressants help decrease shortness of breath, supplemental oxygen is needed during periods of physical exertion.
- **Proton pump inhibitors.** Several commenters wrote that the only effective relief from GI symptoms came from the use of high dose proton pump inhibitors. One commenter shared her concern about the long-term effects of her proton pump inhibitor, although it allows her to “swallow food without throwing up.”

- **Other medications.** Other medications included vasodilators, narcotics, and anticonvulsant medications.
- **Other therapies.** Commenters used several non-drug treatments, consistent with those described by meeting participants. Other commenters mentioned use of dietary and lifestyle changes, dental procedures, and supplemental oxygen. Some commenters had adopted restrictive diets (or were willing to do so) to alleviate GI symptoms; some reported success, but others did not.

Submitted Comments on Ideal Treatments

Commenters were generally in agreement on what the ideal treatment effect would be—namely, to slow or at least halt the progression of their systemic sclerosis. Commenters also expressed the need for more treatment options. One commenter stated, “Scleroderma, and diffuse systemic sclerosis patients [should] be offered homologous stem cell infusion therapy with chemotherapy for treatment options, just like someone with a cancer diagnosis would get.” Another commenter highlighted the need for more treatment options to allow patients to “combat extreme gastro involvement so they can participate in daily life for as long as possible.” One commenter expressed that she has seen little progress in any meaningful reversal of damages, so she must “treat each and every complication with a specialist.”

Conclusion

This Patient-Focused Drug Development meeting for systemic sclerosis provided FDA the opportunity to hear from patients and caregivers directly about the symptoms and the health effects that matter most to patients, the impact that systemic sclerosis has on daily life, and factors that patients consider when selecting a treatment. Systemic sclerosis is a serious condition with physical, emotional, and social impacts. FDA recognizes that patients have a unique ability to contribute to our understanding of their condition and treatment management, and patient perspectives can play a critical role in informing both drug development and regulatory decision making.

The perspectives shared by participants at this meeting provided a vivid portrayal of the challenges and burdens facing individuals with systemic sclerosis. These discussions clearly conveyed that systemic sclerosis can have debilitating physical, emotional and psychological impacts on individuals. They also conveyed the clear need for therapeutic options to better treat the diverse range of symptoms.

FDA is grateful to the individuals who candidly and courageously shared their personal experiences and insights. Through this meeting, FDA learned more about what matters most to the participants regarding their systemic sclerosis on daily life. As Dr. Raj Nair voiced during his closing remarks, “The perspectives and insights... shared [at the meeting] allow [medical product reviewers] to approach [their] role with a better idea of complex needs of the scleroderma patient community.” FDA shares the patient community’s desire and commitment to advancing the development of safe and effective treatment options.

Appendix 1: Meeting Agenda

Public Meeting on Patient-Focused Drug Development for Systemic Sclerosis

October 13, 2020

10:00 - 10:05 am	Welcome Robyn Bent, RN, MS, CAPT, US Public Health Service <i>Office of the Center Director (OCD), Center for Drug Evaluation and Research (CDER), FDA</i>
10:05 - 10:10 am	Opening Remarks Nikolay Nikolov, MD <i>Division of Rheumatology and Transplant Medicine (DRTM), CDER, FDA</i>
10:10 - 10:20 am	Overview of FDA's Patient-Focused Drug Development Initiative Theresa Mullin, PhD <i>Office of the Center Director (OCD), Center for Drug Evaluation and Research (CDER), FDA</i>
10:20 - 10:30 am	Background on Systemic Sclerosis Dinesh Khanna, MD, MSc <i>University of Michigan</i>
10:30 - 10:40 am	Overview of Discussion Format Robyn Bent, RN, MS, CAPT, US Public Health Service <i>OCD, CDER, FDA</i>
10:40 - 11:10 am	Topic 1: Health Effects and Daily Impacts A panel of patients and patient representatives will provide comments to start the discussion on health effects and daily impacts of systemic sclerosis.
11:10 am - 12:15 pm	Large-Group Facilitated Discussion on Topic 1 Patients and patient representatives in the audience are invited to add to the dialogue.

12:15 - 12:45 pm	Break
12:45 - 1:15 pm	<p>Topic 2: Current Approaches to Treatment</p> <p>Patient perspectives on current approaches to treatment for systemic sclerosis. A panel of patients and patient representatives will provide comments to start the discussion.</p>
1:15 - 2:20 pm	<p>Large-Group Facilitated Discussion on Topic 2</p> <p>Patients or patient representatives in the audience are invited to add to the dialogue.</p>
2:20 - 2:25 pm	<p>Closing Remarks</p> <p>Raj Nair, MD</p> <p><i>Division of Rheumatology and Transplant Medicine (DRTM), CDER, FDA</i></p>

DISCUSSION QUESTIONS

Topic 1: Health effects and daily impacts that matter most to patients

1. Which aspects of systemic sclerosis have the most significant impact on your life? (Examples may include tightening of the skin, painful cold sensitivity in hands and feet, i.e. Raynaud's phenomenon, digital ulcers, heartburn, cough, shortness of breath, etc.)
2. Are there specific activities that are important to you but that you cannot do at all or as fully as you would like because of your systemic sclerosis? (Examples of activities may include daily hygiene, engagement in personal relationships, participation in sports or social activities, completion of school or work activities, etc.)
 - a. How does your systemic sclerosis and its impacts affect your daily life on the best days?
 - b. On the worst days?
3. How has your systemic sclerosis changed over time?
 - a. How long have you had symptoms and how long has it been since you were diagnosed with scleroderma?
 - b. Would you define your systemic sclerosis today as being well-managed?
4. What worries you most about your systemic sclerosis?

5. If you could change one thing about your systemic sclerosis, what would it be?

Topic 2: Patients' perspectives on current approaches to treatment

1. What are you currently doing to help treat your systemic sclerosis? (Examples may include prescription medicines, over-the-counter products, and other therapies including non-drug therapies such as diet modification.)
 - a. How has your treatment regimen changed over time, and why?
 - b. What symptom would you most like to be improved or resolved by treatment?
2. How well does your current treatment regimen treat the most significant aspects of your systemic sclerosis? For example, how well do your treatments improve your ability to do specific activities?
3. What are the most significant downsides to your current treatments, and how do they affect your daily life? (Examples of downsides may include time devoted to treatment, side effects of treatment, route of administration, etc.)
4. Assuming there is no complete cure for your systemic sclerosis, what specific things would you look for in an ideal treatment for your systemic sclerosis?
5. What factors do you consider when making decisions about selecting a course of treatment?
6. Efficacy and safety are important for any treatment. When you think about a treatment for your disease:
 - a. Does it make a difference whether:
 - i. the product might improve your most bothersome symptoms or
 - ii. whether the product might preserve organ function, or
 - iii. would you consider improvement in either of those areas equally worth the same level of risk?
 - b. Does your acceptance of potential safety risks go up with the potential effectiveness of a product?
 - c. Is taking a product with the least safety risk or with more efficacy most important?

Appendix 2: Patient and FDA Panel Participants

Patient Panel, Topic 1

- Amy Gietzen, Panelist
- Julie Jeffers, Panelist
- Rosemary Lyons, Panelist
- Amy Harding, Panelist
- Kimberly Bennett-Eady, Panelist

Patient Panel, Topic 2

- Monica Cicchetti, Panelist
- Demi Montgomery, Panelist
- Anita DeVine, Panelist
- Jackie Latka, Panelist
- Susan Nyanzi, Panelist

FDA Panel

- Nikolay Nikolov (Division of Rheumatology and Transplant Medicine (DRTM), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER))
- Rachel Glaser (DRTM, OND, CDER)
- Keith Hull (DRTM, OND, CDER)
- Raj Nair (DRTM, OND, CDER)
- Snezana Trajkovic (Division of Dermatology and Dentistry (DDD), OND, CDER)
- Maryjoy Mejia (DDD, OND, CDER)
- Shera Schreiber (Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT), Office of Tissues and Advanced Therapies (OTAT), Center for Biologics Evaluation and Research (CBER))
- Becky Rothwell (Office of Biostatistics (OB), Office of Translational Sciences (OTS), CDER)
- Onyeka Illoh (Division of Clinical Outcome Assessments (DCOA), OND, CDER)

Appendix 3: Meeting Polling and Scenario Questions

The following questions were posed to participants at various points throughout the October 13, 2020 public meeting on Patient-Focused Drug Development for Systemic Sclerosis. Participation in the polling questions was voluntary. The results were used as a discussion aid only and should not be considered scientific data.

Demographic Questions

1. Do you live in the Washington, D.C. metropolitan area (including the Virginia and Maryland suburbs)?
 - a. Yes
 - b. No

2. Have you or your loved one ever been diagnosed as having systemic sclerosis?
 - a. Yes
 - b. No

We will ask that the remainder of the questions be answered by people who responded “yes” to Question 2. Please answer for the person diagnosed with systemic sclerosis.

3. What is your age?
 - a. Younger than 18
 - b. 18 – 30
 - c. 31 – 40
 - d. 41 – 50
 - e. 51 – 60
 - f. 61 – 70
 - g. 71 or greater

4. Do you identify as:
 - a. Female
 - b. Male
 - c. Other

5. What is the length of time since your diagnosis?
 - a. Less than 1 year ago
 - b. 1 years ago to 5 years ago
 - c. 5 years ago to 10 years ago
 - d. More than 10 years ago
 - e. I’m not sure

6. Which subtype of systemic sclerosis have you been diagnosed with? **Select all that apply.**
- a. Diffuse (Skin tightening or thickening affects large areas of the body; organ damage to GI tract, kidneys, lungs, and heart; pain or arthritis; high blood pressure)
 - b. Limited (Skin tightening or thickening is limited to fingers, hands, or face; heartburn; Raynaud's phenomenon; pain or arthritis; CREST syndrome; red spots on the body as a result of enlarged blood vessels)
 - c. Sine (Symptoms of organ disease including Raynaud's phenomenon, but no skin thickening)
 - d. Systemic sclerosis with overlap syndrome (Overlap of features of another systemic rheumatic disease such as systemic lupus erythematosus (SLE), rheumatoid arthritis, polymyositis, or Sjögren's syndrome)
 - e. Other
 - f. I'm not sure

Questions for Topic 1: Health Effects and Daily Impacts

7. Of all the symptoms you have experienced because of your systemic sclerosis, which do you consider to have the most significant impact on your daily life? **Please choose up to three symptoms.**
- a. Hardening or tightening of patches of skin
 - b. Skin thickening
 - c. Digital ulcers
 - d. Painful cold sensitivity in hands and/or feet (Raynaud's phenomenon)
 - e. Heartburn or difficulty swallowing
 - f. Digestive symptoms (cramps, bloating, diarrhea, constipation)
 - g. Arthritis
 - h. Fatigue
 - i. Other symptom not mentioned
8. Of all the symptoms you have experienced because of your systemic sclerosis, which **single symptom** do you consider to be most bothersome?
- a. Hardening or tightening of patches of skin
 - b. Skin thickening
 - c. Digital ulcers
 - d. Painful cold sensitivity in hands and/or feet (Raynaud's phenomenon)
 - e. Heartburn or difficulty swallowing
 - f. Digestive symptoms (cramps, bloating, diarrhea, constipation)
 - g. Arthritis
 - h. Fatigue
 - i. Other symptom not mentioned
9. Which aspects of daily functioning or movement are most affected by your systemic sclerosis? **Please choose up to three answers.**

- a. Ability to sleep
- b. Ability to move hands and fingers (such as hold objects or button a shirt)
- c. Ability to walk
- d. Ability to breathe
- e. Ability to eat
- f. Ability to complete household tasks
- g. Ability to complete professional and work tasks
- h. Emotional or psychological impacts (such as anxiety, fear, or depression)
- i. Other impacts not mentioned

Questions for Topic 2: Current Treatment Approaches

10. Have you ever used any of the following interventions or medical products (drug therapies or medical devices) to treat your systemic sclerosis? **Check all that apply.**

- a. Medications to modify blood flow (such as nifedipine)
- b. Medications that suppress the immune system to prevent organ rejection and/or treat arthritis (such as Cyclosporine, Azathioprine)
- c. Antifibrotic medications for interstitial lung disease (such as nintedanib)
- d. Corticosteroids for skin and arthritis symptoms (such as prednisone)
- e. Proton-pump inhibitors for digestive symptoms (such as omeprazole)
- f. Painkillers (such as Vicodin, Percocet, OxyContin)
- g. Bone marrow or Solid Organ transplant
- h. Other medical products or interventions not mentioned
- i. I'm not using any medical products or interventions

11. Besides the medical products or interventions mentioned previously, what else are you doing to manage your systemic sclerosis? **Check all that apply.**

- a. Over the counter medications (such as ibuprofen, acetaminophen)
- b. Lotions and moisturizers
- c. Physical therapy and exercise
- d. Diet modifications (such as keto diet, paleo diet, vegan diet, etc.)
- e. Counseling or psychological treatment
- f. Other therapies not mentioned
- g. I am not doing or taking any therapies to manage my systemic sclerosis

12. For the medical products or interventions you use, what about the treatment bothers you the most? **Please choose up to three answers.**

- a. How the medication is administered (such as a topical cream, injection, or an oral medication)
- b. The treatment only provides minimal benefit
- c. The treatment is effective only for a short-term
- d. Bothersome side effects of the treatment
- e. Concern about serious risks of the treatment
- f. Uncertainty about long-terms effects of treatment

- g. Difficulty in accessing treatment (such as insurance or physician referral)
- h. Other negative impacts not mentioned

HYPOTHETICAL SCENARIO

Imagine that a new self-injectable medication indicated to treat systemic sclerosis has recently been approved by FDA. Your doctor believes that you may be a good candidate for this medication.

In the clinical trials that were conducted, the medication was shown to reduce the symptom that most significantly impacts your daily life when injected once weekly.

More common side effects of this therapy may include headache, diarrhea, nausea, stomach or abdominal pain, and weight loss. Rarer but more serious side effects may include infection, seizures, trouble breathing, fever, general feeling of discomfort or illness, and risk of bleeding.

Given the risks and benefits, would you take this medication?

- a. Yes
- b. No
- c. Maybe