AMRYT VIRTUAL CAPITAL MARKETS EVENT

September 13, 2021

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DR. JOE WILEY, CEO - WELCOME & INTRODUCTION

AMRYT MANAGEMENT TEAM IN ATTENDANCE

COMPRISED OF INDUSTRY LEADERS IN RARE DISEASES

DR. JOE WILEY
CEO

SHEILA FRAME
President Americas

RORY NEALON
COO/CFO

DR. TRACY CUNNINGHAM
VP Head of Development

DR. MARK SUMERAY
Chief Medical Officer

DR. GERRY GILLIGAN
VP Manufacturing Supply Chain

DR. HELEN PHILLIPS
Head Of Medical Affairs

PAUL GREENLAND
President EMEA Region

SEPTEMBER 13, 2021 - AGENDA

Time (Eastern)		
1000 - 1005	Introduction & Overview	Dr. Joe Wiley, CEO
1005 - 1025	KOL - Epidermolysis Bullosa Discussion	Dr. Harper Price, MD, FAAD, FAAP, Phoenix Children's Hospital
1025 - 1050	Oleogel-S10 Update • Overview of Clinical Data • Regulatory Pathways • Launch Plans	Dr. Tracy Cunningham, VP Head of Development Sheila Frame, President, Americas
1050 - 1115	KOL - Acromegaly Discussion	Dr. Maria Fleseriu, MD, FACE, Oregon Health & Science University

1115 - 1145	Mycapssa®
	• Acromegaly
	  • Market Opportunity
	  • US Expansion Plans
	• NET - Pipeline Opportunities
	• Regulatory Pathways
	• Synergy Achievement Plans
		Sheila Frame, President, Americas
		
		Dr. Mark Sumeray, CMO
		
		Rory Nealon, CFO / COO

1145 - 1200	Q&A Session	Dr. Joe Wiley, Dr. Mark Sumeray, Rory Nealon, Sheila Frame, Dr. Helen Philips, Dr. Tracy Cunningham, Paul Greenland, Dr. Gerry Gilligan

DR. HARPER PRICE – EPIDERMOLYSIS BULLOSA DISCUSSION

DR. HARPER PRICE

PHOENIX CHILDREN'S®

Harper Price, MD completed her dermatology training at Penn State Milton S. Hershey Medical Center in Hershey, Pennsylvania, and her pediatric dermatology fellowship at New York University Medical Center, New York. She has served at Phoenix Children's Hospital (PCH) since 2009 where she provides the latest medications and technology available for the specialized treatment of infants, children, adolescents and young adults affected by large nevi.

Shortly after joining PCH, she became the program director of their pediatric dermatology fellowship. She now serves as Associate Chief of the Division of Dermatology.

While a student, Dr. Price worked closely with doctors at NYU to review all the major nevus registries in existence at the time and undertook to combine all the data into a single collection. Nevus Outreach invited Dr. Price to attend and assist at the 2010 conference. Based on the strength of her work, she was invited to speak at the 2011 International Expert Meeting for Large Congenital Melanocytic Nevi and Neurocutaneous Melanocytosis in Tübingen, Germany, where she was recruited to serve as Assistant Director of a team of world experts to oversee creation of an all-new world-wide nevus patient data repository under the direction of Dr. Veronica Kinsler at Great Ormond Street Hospital in London. Dr. Price is a regular speaker at national dermatology and pediatric conferences. Her work is published in textbooks and peer-reviewed journals.

Epidermolysis Bullosa: Disease State Awareness & Burden

Harper N. Price, MD, FAAD, FAAP

Phoenix Children's Hospital

Epidermolysis bullosa was first described in 1870, yet there is no FDA approved treatment or effective clinical standard of care today.

EB is a rare disease

“EB” encompasses a group of genetic conditions with skin fragility as a main clinical finding.

Has et al. BJD. 2020

Classical types of EB Level of skin cleavage	EB type	Inheritance	Mutated gene(s)	Targeted protein(s)
Intraepidermal	EB simplex	Autosomal dominant	*KRT5, KRT14*	Keratin 5, keratin 14
			PLEC	Plectin
			KLHL24	Kelch-like member 24
		Autosomal recessive	*KRT5, KRT14*	Keratin 5, keratin 14
			DST	Bullous pemphigoid antigen 230 (BP230) (syn. BPAG1e, dystonin)
			EXPH5 (syn. *SLAC2B*)	Exophilin-5 (syn. synaptotagmin-like protein homolog lacking C2 domains b, Slac2-b)
			PLEC	Plectin
			CD151 (syn. *TSPAN24*)	CD151 antigen (syn. tetraspanin 24)
Junctional	Junctional EB	Autosomal recessive	*LAMA3, LAMB3, LAMC2*	Laminin 332
			COL17A1	Type XVII collagen
			ITGA6, ITGB4	Integrin α6β4
			ITGA3	Integrin α3 subunit
Dermal	Dystrophic EB	Autosomal dominant	*COL7A1*	Type VII collagen
		Autosomal recessive	*COL7A1*	Type VII collagen
Mixed	Kindler EB	Autosomal recessive	*FERMT1* (syn. *KIND1*)	Fermitin family homolog 1 (syn. kindlin-1)

Types of EB are classically divided by where the fragility is in the skin

EB simplex is the most common type of EB.

Most common EBS clinical subtypes	Targeted protein(s)
Autosomal dominant EBS	
Localized	Keratin 5, keratin 14
Intermediate	Keratin 5, keratin 14
Severe	Keratin 5, keratin 14
With mottled pigmentation	Keratin 5[a]
Migratory circinate erythema	Keratin 5
Intermediate	Plectin
Intermediate with cardiomyopathy	**Kelch-like member 24**
Autosomal recessive EBS	
Intermediate or severe	Keratin 14, keratin 5
Intermediate	Plectin
Localized or intermediate with BP230 deficiency	Bullous pemphigoid antigen 230 (BP230) (syn. BPAG1e)
Localized or intermediate with exophilin-5 deficiency	Exophilin-5 (syn. Slac2-b)
Intermediate with muscular dystrophy	**Plectin**
Severe with pyloric atresia	**Plectin**
Localized with nephropathy	**CD151 (CD151 antigen) (syn. tetraspanin 24)**

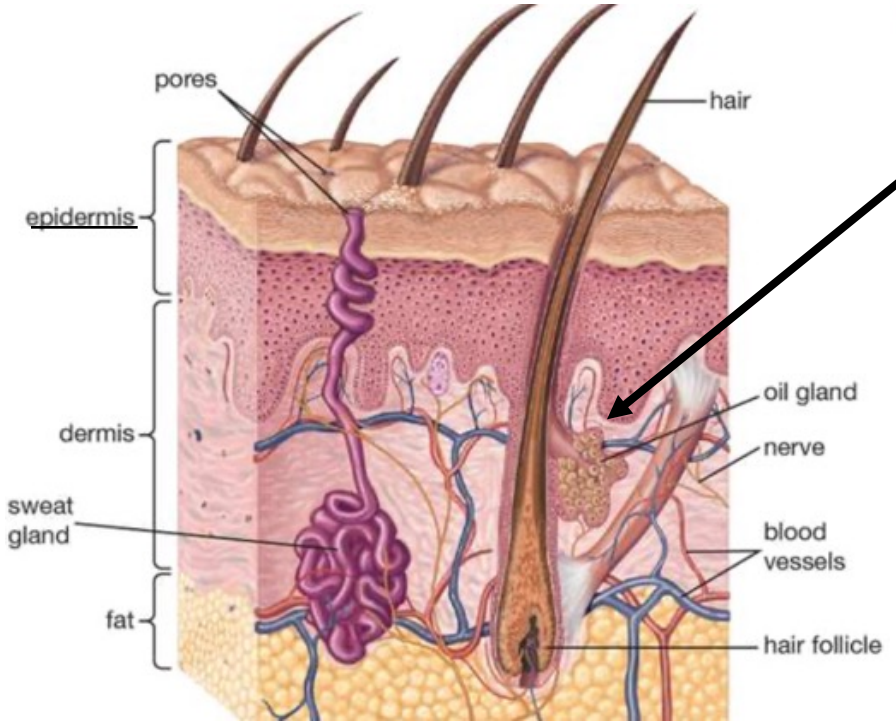
[a]Typical recurrent mutation in keratin 5, but cases with other keratin 5, keratin 14 or exophilin-5 mutations have been reported; **bold**, syndromic EBS subtypes.

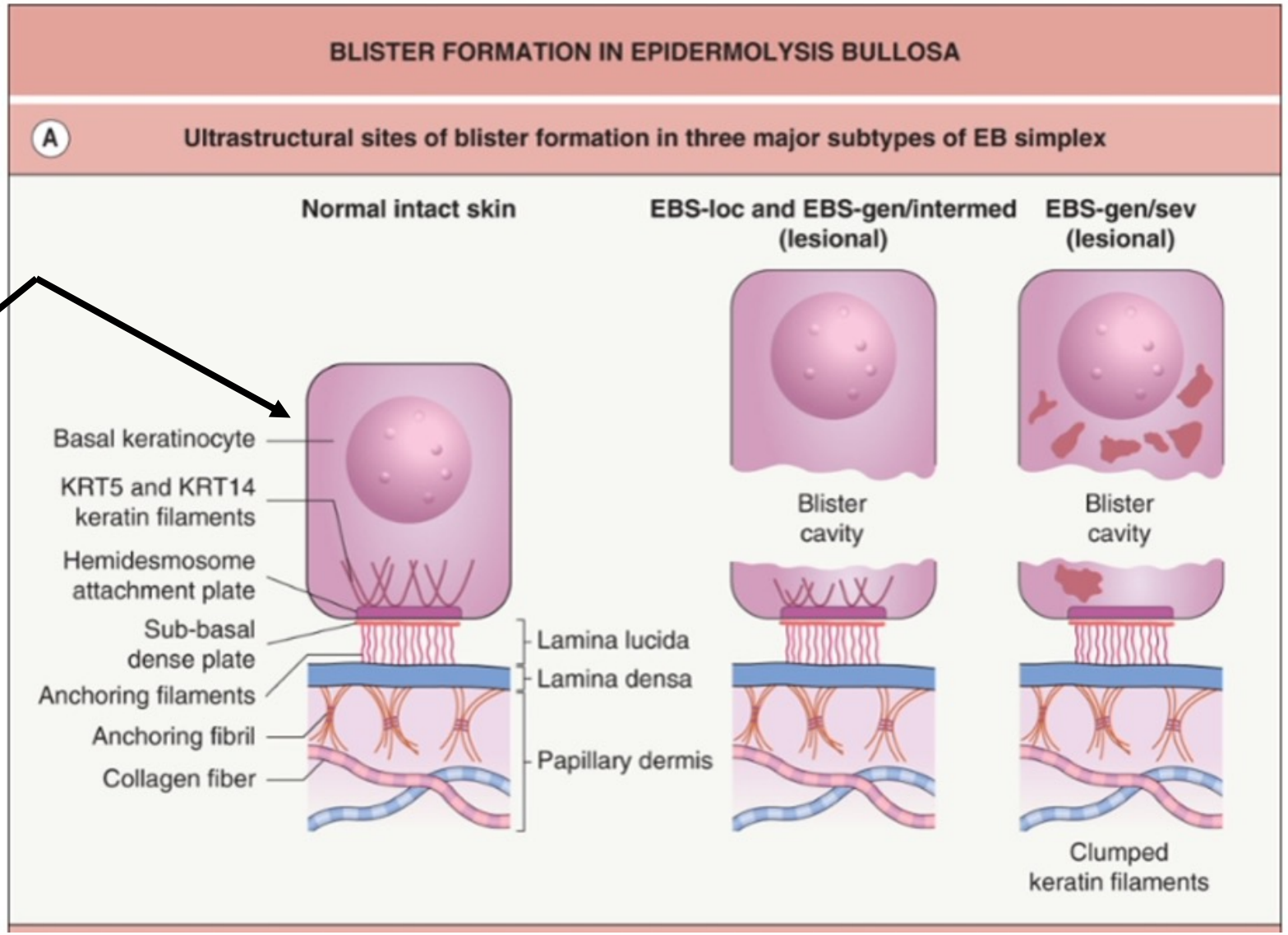
- Skin cleavage in basal layer of keratinocytes
- Several types of EBS
  - Keratin 5, 14
- Autosomal dominant, recessive
- Skin and other organ systems
- *New genes CD151 and KLHL24*

Phoenix Children's Hospital

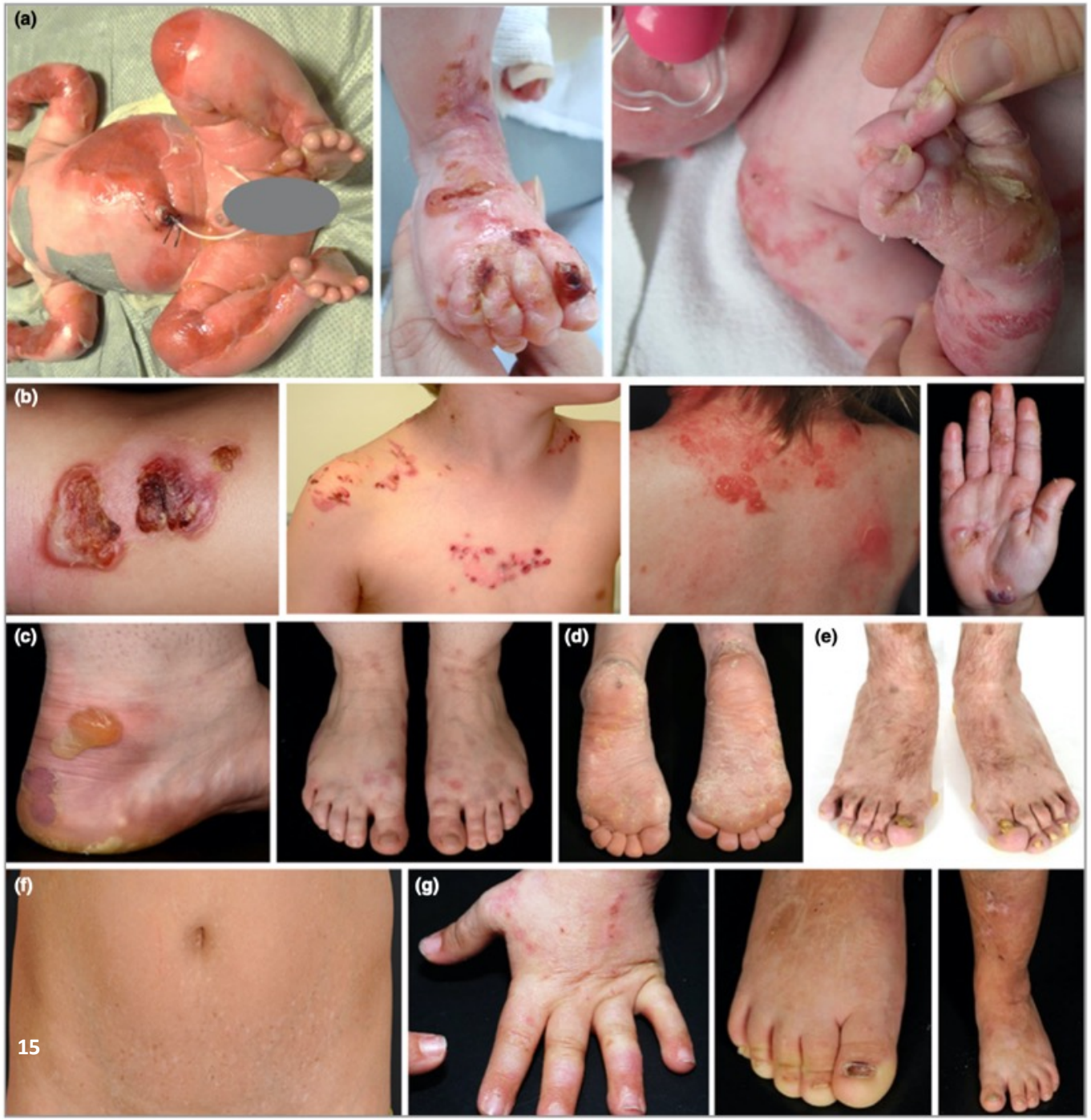
Has et al. BJD. 2020

EB simplex blisters occur in the basal layer of the epidermis.





https://www.britannica.com/science/human-skin



- ✓ Blisters, ulceration, crust (scabs)
- ✓ Clusters of blisters, blood blisters
- ✓ Thick, dystrophic nails
- ✓ Keratoderma
- ✓ Atrophic scarring (estim 15%)

Has et al. BJD. 2020

Junctional EB is the least common subtype.

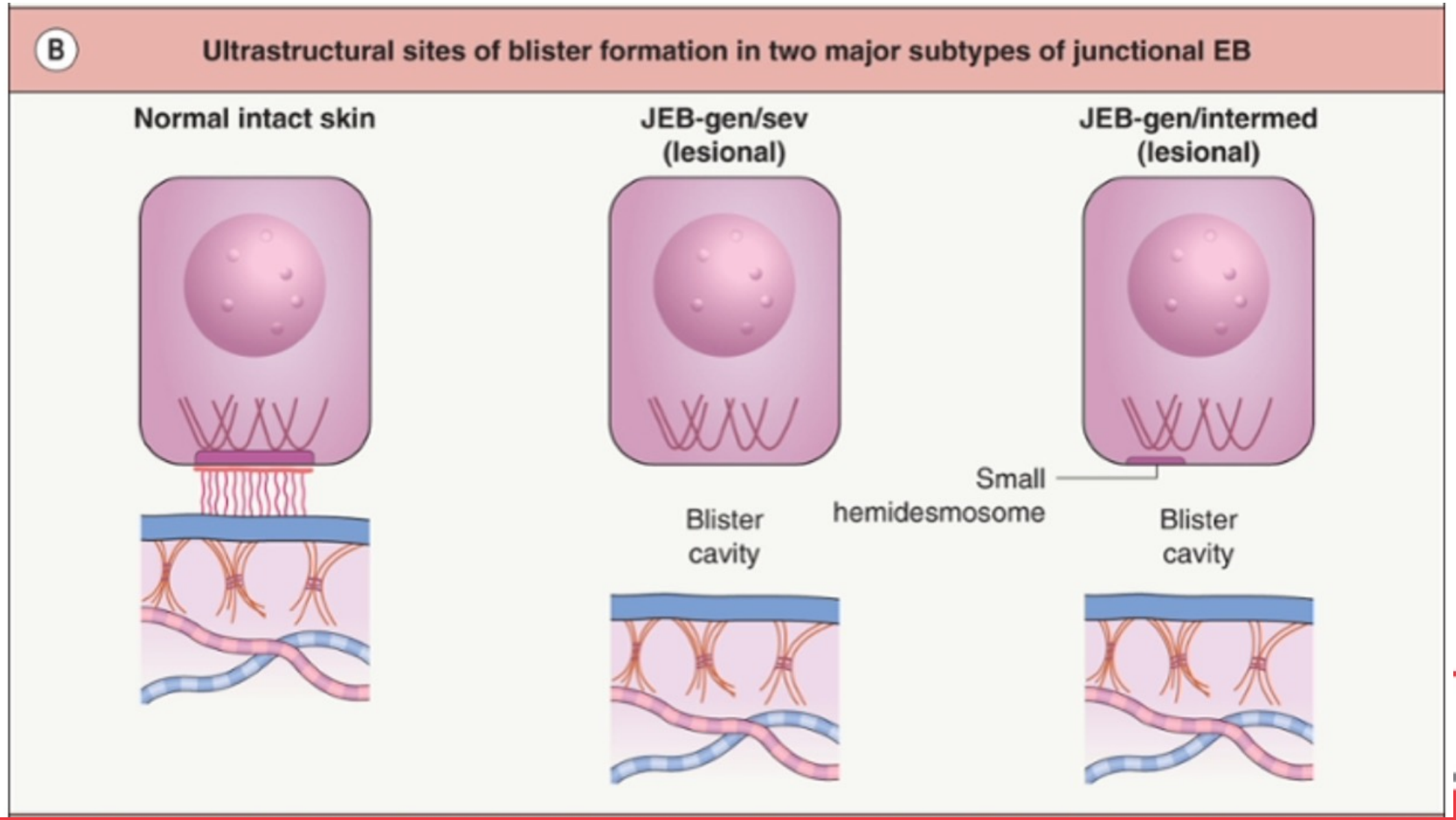
Most common JEB clinical subtypes	Targeted protein(s)
Severe	Laminin 332[a]
Intermediate	Laminin 332
Intermediate	Type XVII collagen
With pyloric atresia	**Integrin α6β4**
Localized	Laminin 332, type XVII collagen, integrin α6β4, integrin α3 subunit
Inversa	Laminin 332
Late onset	Type XVII collagen
LOC syndrome	Laminin α3A
With interstitial lung disease and nephrotic syndrome	**Integrin α3 subunit**

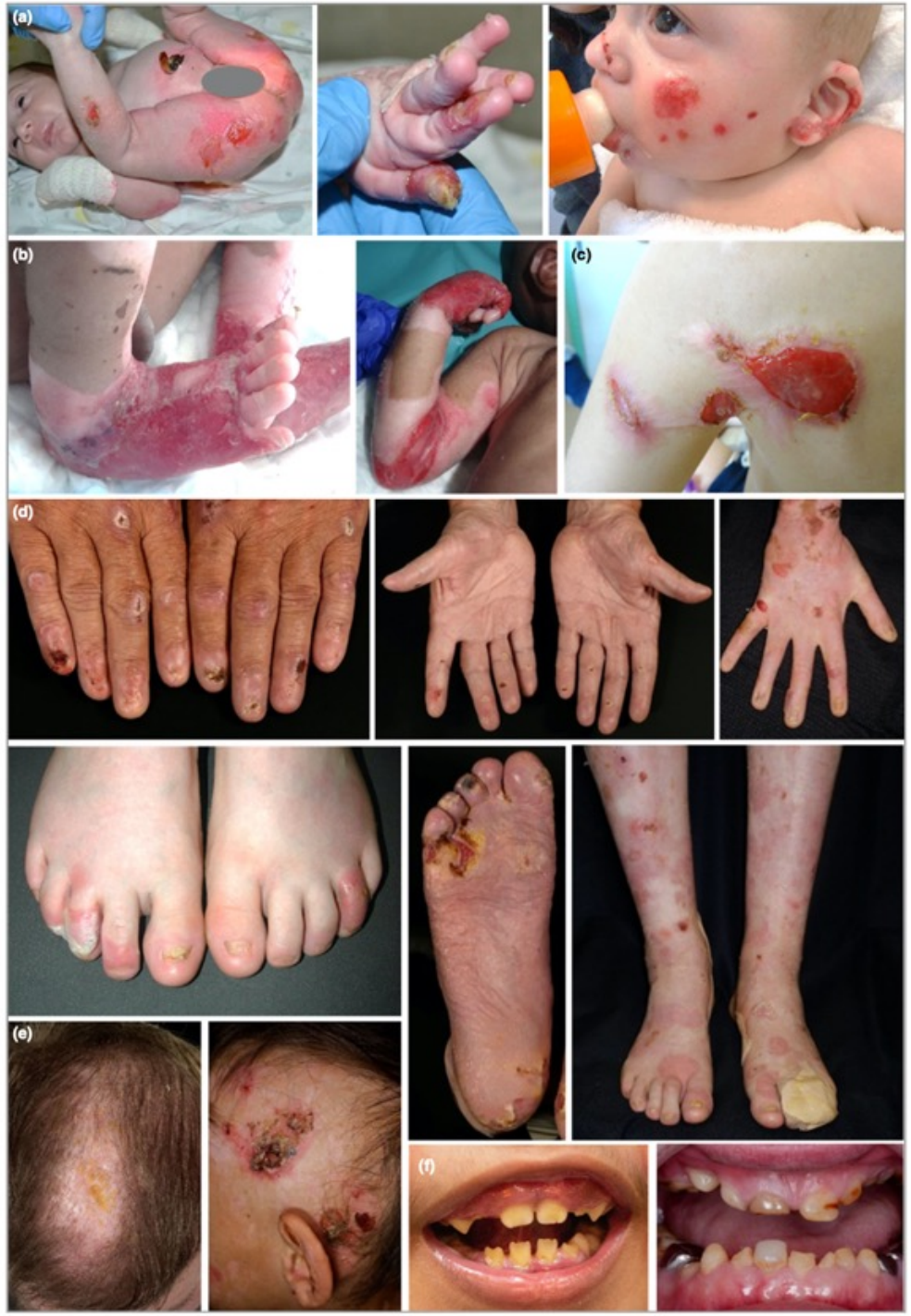
LOC, laryngo–onycho–cutaneous. [a]JEB severe is rarely caused by pathogenic variants affecting the type XVII collagen gene; **bold**, syndromic JEB subtypes.

- Autosomal recessive
- Skin cleavage: lamina lucida of the basement membrane
- Intermediate, severe
- Severe type early lethality

Has et al. BJD. 2020

JEB blisters occur in the lamina lucida.





- ✓ Granulation tissue on the distal digits, face, ears
- ✓ Hoarse cry
- ✓ Skin blistering and crusts (scabs)
- ✓ Nail loss and dystrophy
- ✓ Scarring
- ✓ Alopecia (hair loss)
- ✓ Dental enamel defects (discolored, pitted teeth)

Has et al. BJD. 2020

Dystrophic EB is caused by mutations in the gene encoding **collagen VII**, *COL7A1*.

DEB subtypes	Targeted protein
Autosomal dominant DEB (DDEB)	
Intermediate	Type VII collagen
Localized	
Pruriginosa	
Self-improving	
Autosomal recessive DEB (RDEB)	
Severe	Type VII collagen
Intermediate	
Inversa	
Localized	
Pruriginosa	
Self-improving	
Dominant and recessive (compound heterozygosity)	
DEB, severe	Type VII collagen

bold, most common subtypes.

- AR and AD
- RDEB is more severe
- Overlap exists
- Milia and scarring
- Secondary complications

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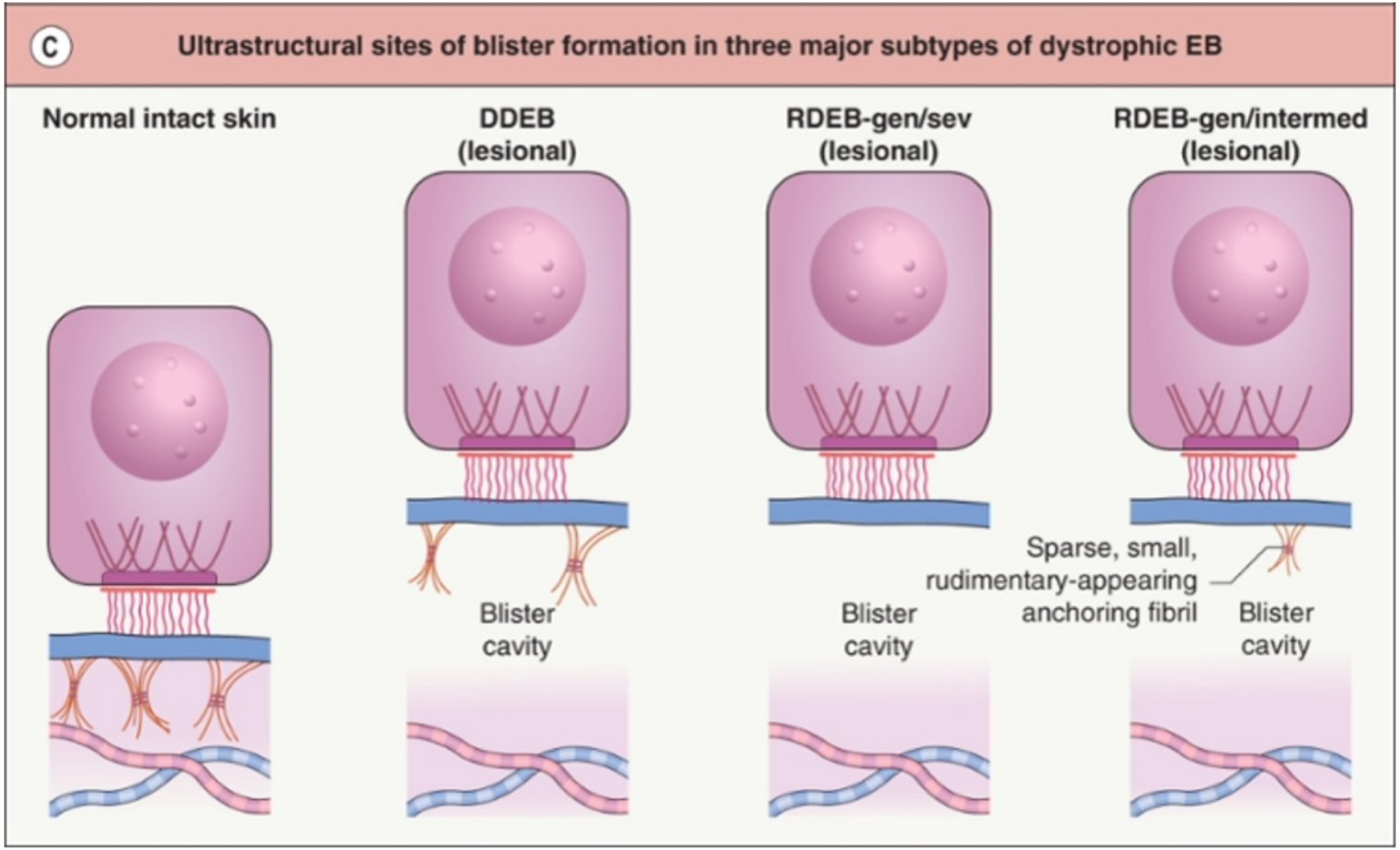
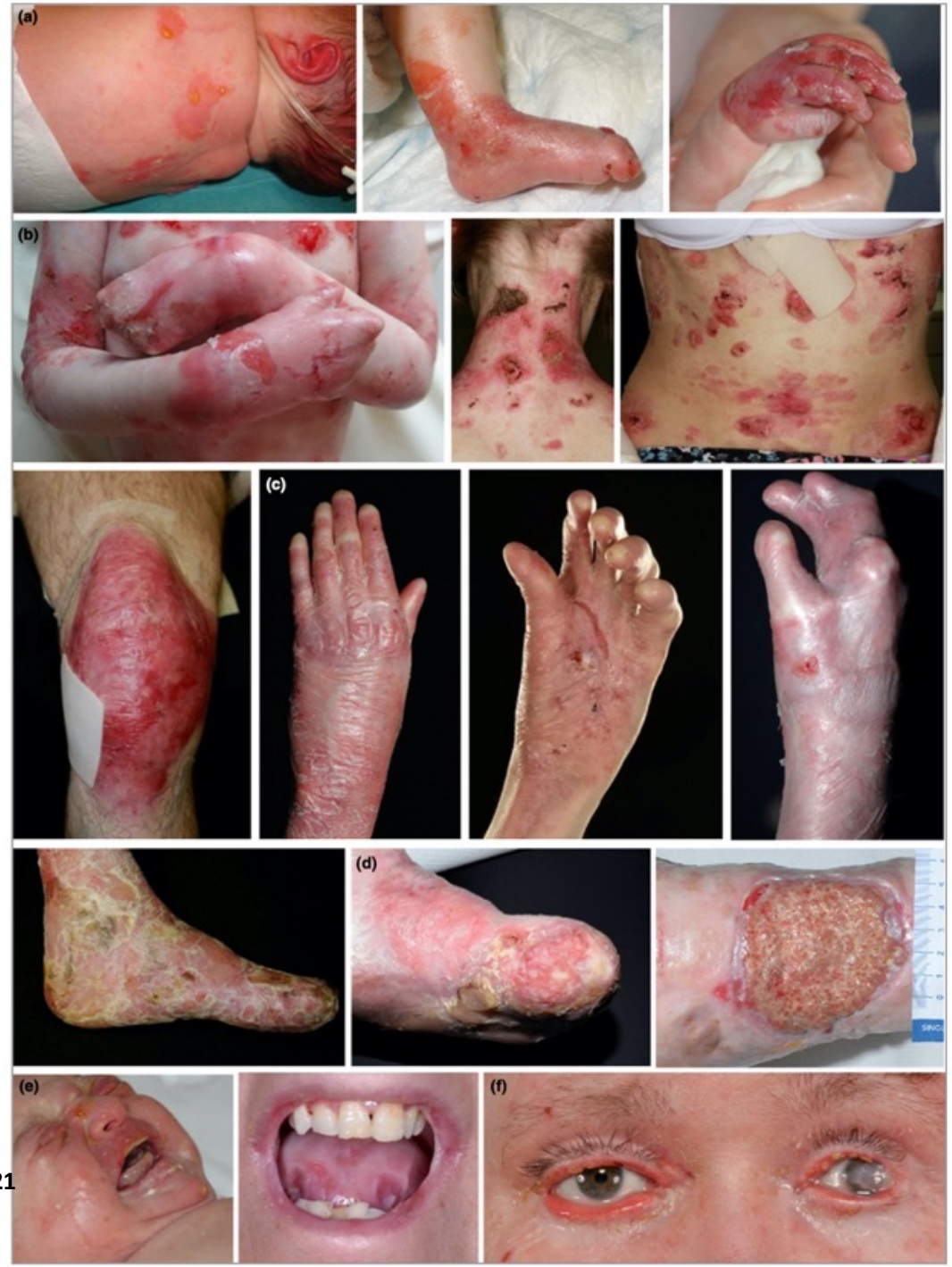
Has et al. BJD. 2020

Collagen VII is the major anchoring fibril in the basement membrane zone of the skin.

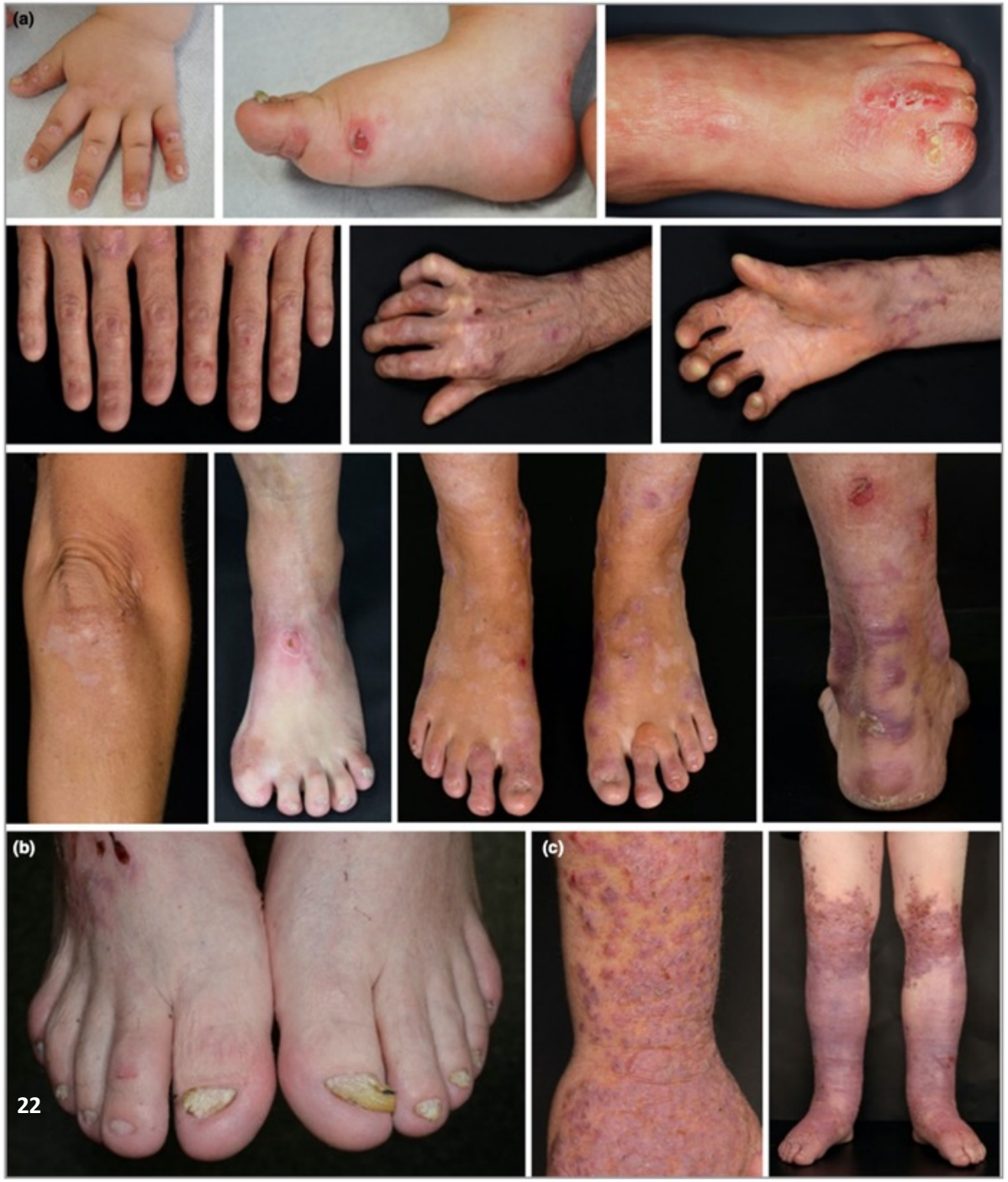




Severe RDEB

- ✓ Widespread skin fragility, ulceration early in life
- ✓ Scarring associated with milia
- ✓ Joint contractures, flexion contractures
- ✓ Loss of distal digits, digital fusion
- ✓ Squamous cell carcinoma development
- ✓ Oral blistering, small mouth opening, dental caries
- ✓ Ectropion, corneal abrasions and scarring

Has et al. BJD. 2020



Dominant DEB, Intermediate RDEB

- ✓ Often overlap in appearance
- ✓ Blisters over acral sites and bony areas
- ✓ Scarring, may be with milia
- ✓ Nail dystrophy or loss of nails
- ✓ Thickened skin on fingers, palms may cause contractures

Diagnosis is based on clinical information and molecular genetic testing.

- Bedside exam→ *where it starts*
- Family history, personal history
- Presence or absence of clinical findings (scarring, milia)
- *Past→ induce a blister for biopsy X 2*
  - *Immunomapping, electron microscopy (EM)*
- *Current→ genetic testing (blood, cheek swab)*

Epidermolysis Bullosa (EB) XomeDx® *Slice*

ADD TO ORDER

FORMS AND DOCUMENTS

Test Info Sheet Test Requisition Form

TEST DETAILS

GENES: Expand Genes

CD151, CDSN, CHST8, COL17A1, COL7A1, CSTA, DSG1, DSP, DST, EXPH5, FERMT1, FLG2, ITGA3, ITGA6, ITGB4, JUP, KLHL24, KRT1, KRT10, KRT14, KRT5, LAMA3, LAMB3, LAMC2, PKP1, PLEC, SERPINB8, TGM5

DISORDERS:

- Acral Peeling Skin Syndrome
- Dystrophic Epidermolysis Bullosa (DEB)
- Epidermolysis Bullosa (EB)
- Epidermolysis Bullosa Dystrophica
- Epidermolysis Bullosa Simplex
- Epidermolysis Bullosa, Junctional Type
- Epidermolysis Bullosa, Junctional with Muscular Dystrophy
- Epidermolysis Bullosa, Junctional with Pyloric Atresia
- Generalized Atrophic Benign Epidermolysis Bullosa (GABEB)
- Herlitz Junctional Epidermolysis Bullosa
- Mitis Junctional Epidermolysis Bullosa
- Non-Herlitz Junctional Epidermolysis Bullosa

CLINICAL UTILITY:

- Identification of the specific molecular basis of a hereditary blistering disorder
- Genetic counseling and recurrence risk assessment
- Preparation for prenatal testing in future pregnancies

NOTES:

If an affected individual is found by XomeDxSlice-EB to have only a single mutation in a gene with recessive inheritance, deletion/duplication analysis of that gene can be performed at no additional cost.

Patient samples sent for XomeDxSlice will not be evaluated for secondary findings and therefore will not receive secondary findings as part of their result.

LAB METHOD:

- Next-Gen Sequencing

NEW YORK CLIENTS

Tests displaying the status "New York Approved: Yes" are approved or conditionally approved by New York State and do not require an NYS "NPL" exemption. Please note, for carrier/targeted variant tests the approval status depends on whether the gene is in an approved GeneDx single-gene or multi-gene test. In addition, carrier/targeted testing for any gene is automatically approved for relatives of existing GeneDx patients. In all other situations, complete the New York Exemption Form and fax it to the NYS Department of Health to obtain case-by-case permission before shipping the specimen to GeneDx.

NYS Dept. of Health Instructions
New York Exemption Form

VIEW TESTS

FEATURED TESTS

XomeDx
XomeDxSlice
Hereditary Cancer
Neurology/Mitochondrial Genetics
Cardiology Genetics
Prenatal Genetics
Deletion/Duplication Analysis
Carrier/Mutation-Specific Testing
Cytogenetics

Molecular genetic testing for EB is [likely] the new gold standard.

- Allows for precise subtype information and prognosis
  - Clinical diagnosis is unreliable
- Immunomapping and EM are not always accurate
- Little phenotypic correlation and no subtype information previously
- Allows for inclusion into clinical trials, treatments, natural history
- Genetic counseling and prenatal diagnosis

EB disease process is complex.

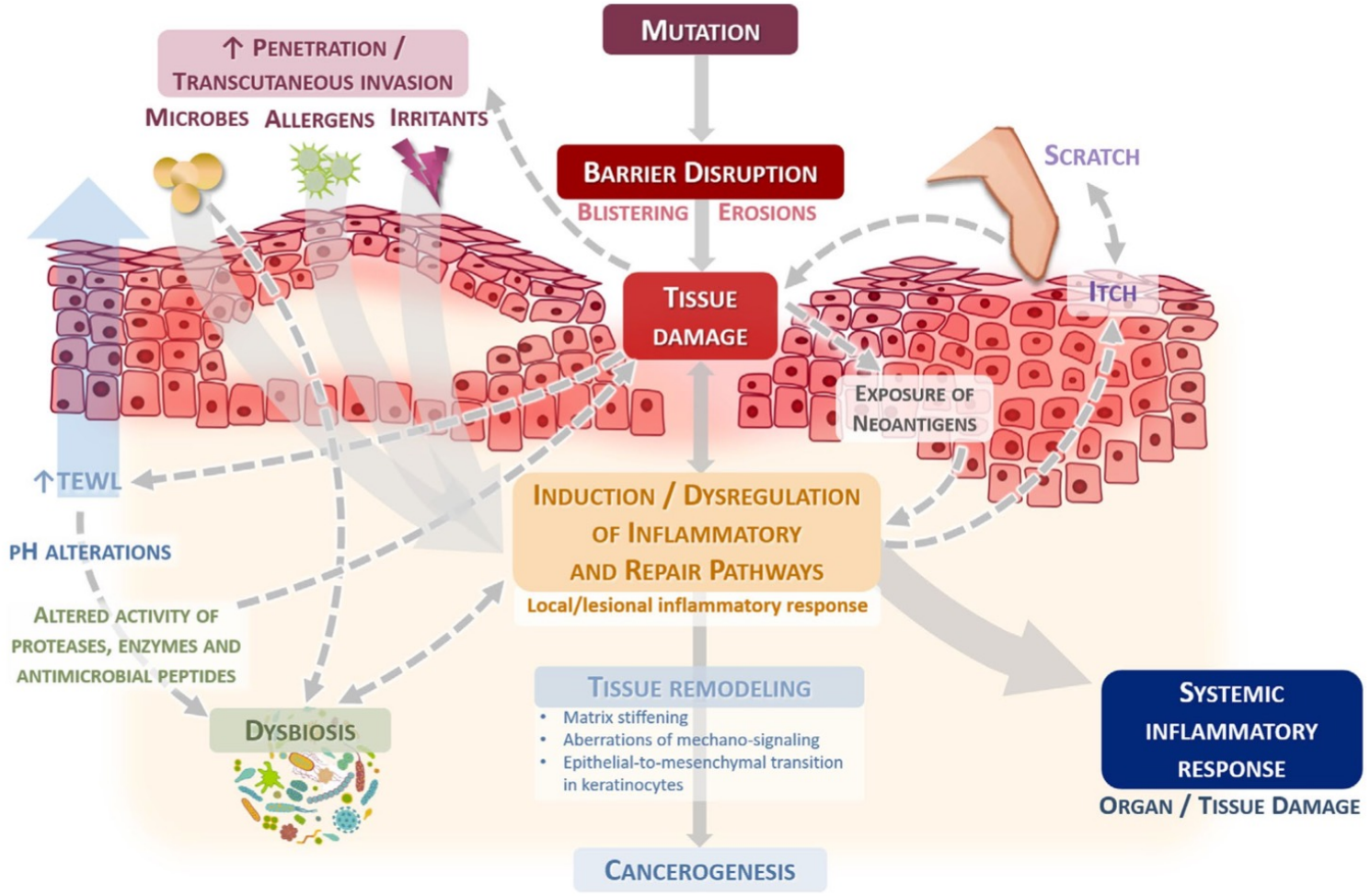


FIGURE 1 Epidermolysis bullosa is characterized by a genetically determined barrier disruption with chronic tissue damage. This is implicated to favour induction, perpetuation and dysregulation of pro- and autoinflammatory responses, causing microenvironmental alterations, dysbiosis and tumorigenic tissue remodelling

Phoenix Children's Hospital

From: Prodinger, Bauer, Laimer. Exper Dermatol. 2020

The standard of care for EB is wound care and maximizing wound management.

- Prevention and treatment of infection (localized to sepsis)
- Protect from further injury, trauma
- Facilitate wound healing
- Limit, treat pain and itch
- Monitor for skin cancer (RDEB) and stalled wounds
- Lab monitoring for end organ damage, malnutrition

Many forms of EB do not just involve the skin.

- Eye involvement, blindness
- Anemia (chronic/iron)
- Urethral strictures
- Elevated systemic inflammation
- Malnutrition, vitamin deficiencies
- Constipation, malabsorption, anal fissures
- Esophageal strictures, reflux
- Cardiomyopathy
- Joint contractures
- Oral disease, poor dentition
- Airway disease
- Kidney and lung disease
- Delayed puberty
- Osteopenia, osteoporosis

EB multidisciplinary care by a team is ideal.

- **Dermatologists (pediatric/adult)**
- **Dedicated EB nurse**
- **Clinic coordinator**
- **Pain management**
- **Occupational/Physical Therapy**
- **Nutrition**
- **Social worker/case management**

- Gynecology
- Psychology/psychiatry
- Palliative care
- Surgical subspecialists
- Gastroenterology
- Hematology/oncology
- Dental
- Hospital medicine
- Endocrinology
- Rehab medicine
- Ophthalmology
- Nephrology/Urology

There are many unmet needs for patients with EB.

- Limited access to testing and chronic need for supplies ($$$)
- Few EB centers in USA and limited number of experts (transition?)
- Localized treatments to heal wounds
- Generalized disease modifying drugs
  - *Not just for the skin!*
- Drugs to alleviate itch/pain

Financial impact for patients is burdensome.

Financial burden of epidermolysis bullosa on patients in the United States

- Bandage coverage and cost is variable in the US
  - Out of pocket costs for wound care supplies $$$
    - 26% respondents spent >$1000 monthly*
  - Limited insurance coverage
- *73% Major or moderate financial impact (severe subtypes)

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*E. Gorrell at el. Pediatr Derm 2020

The challenges of living with and managing epidermolysis bullosa: insights from patients and caregivers

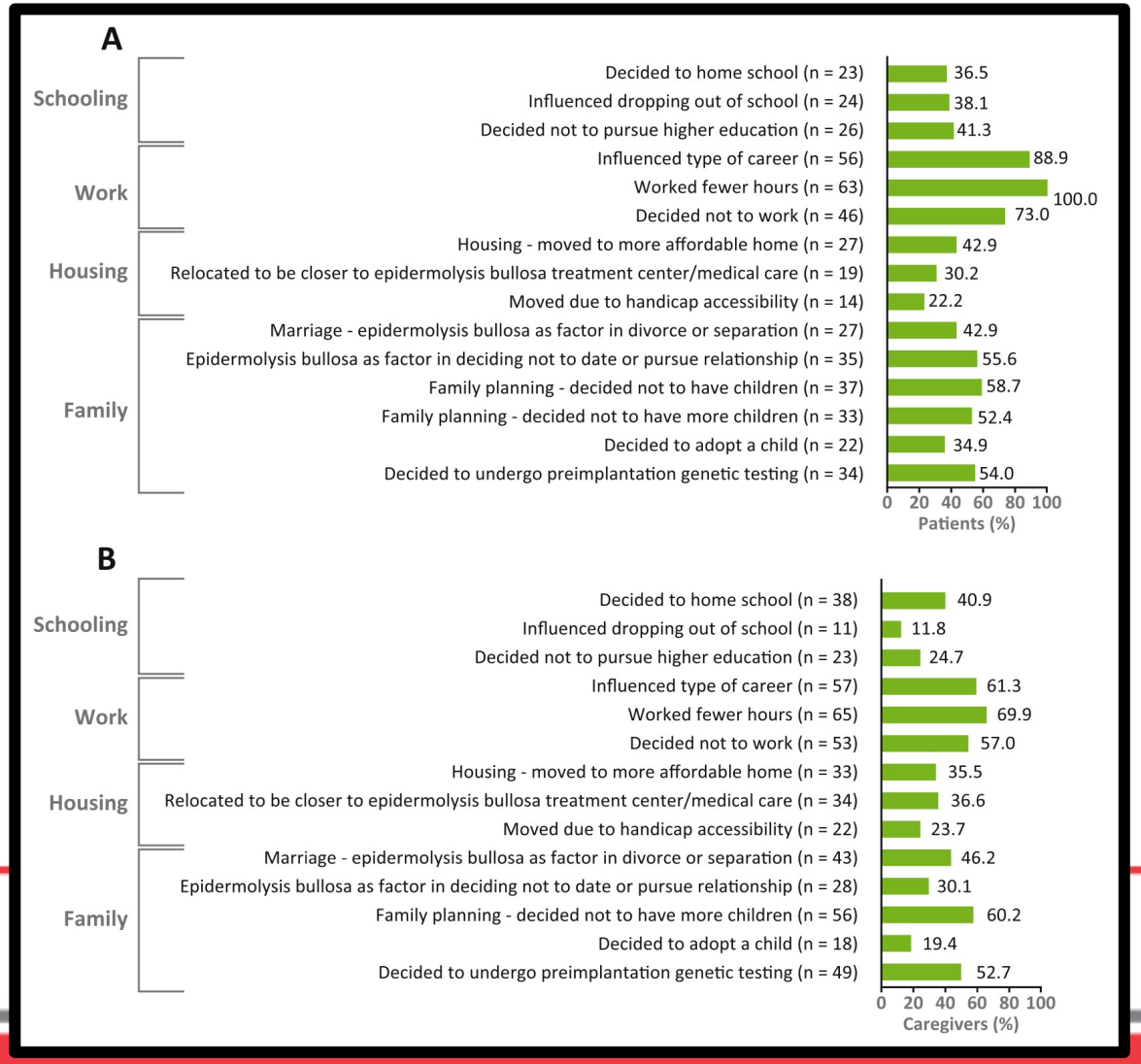
Anna L. Bruckner[1*], Michael Losow[2], Jayson Wisk[2], Nita Patel[2], Allen Reha[2], Hjalmar Lagast[2], Jamie Gault[2], Jayne Gershkowitz[2], Brett Kopelan[3], Michael Hund[4] and Dedee F. Murrell[5]

90 Question Survey

156 responses (patients/caregivers)

Impact on:

- Education
- Career
- Home life
- QOL (neg)
- Finances (neg)



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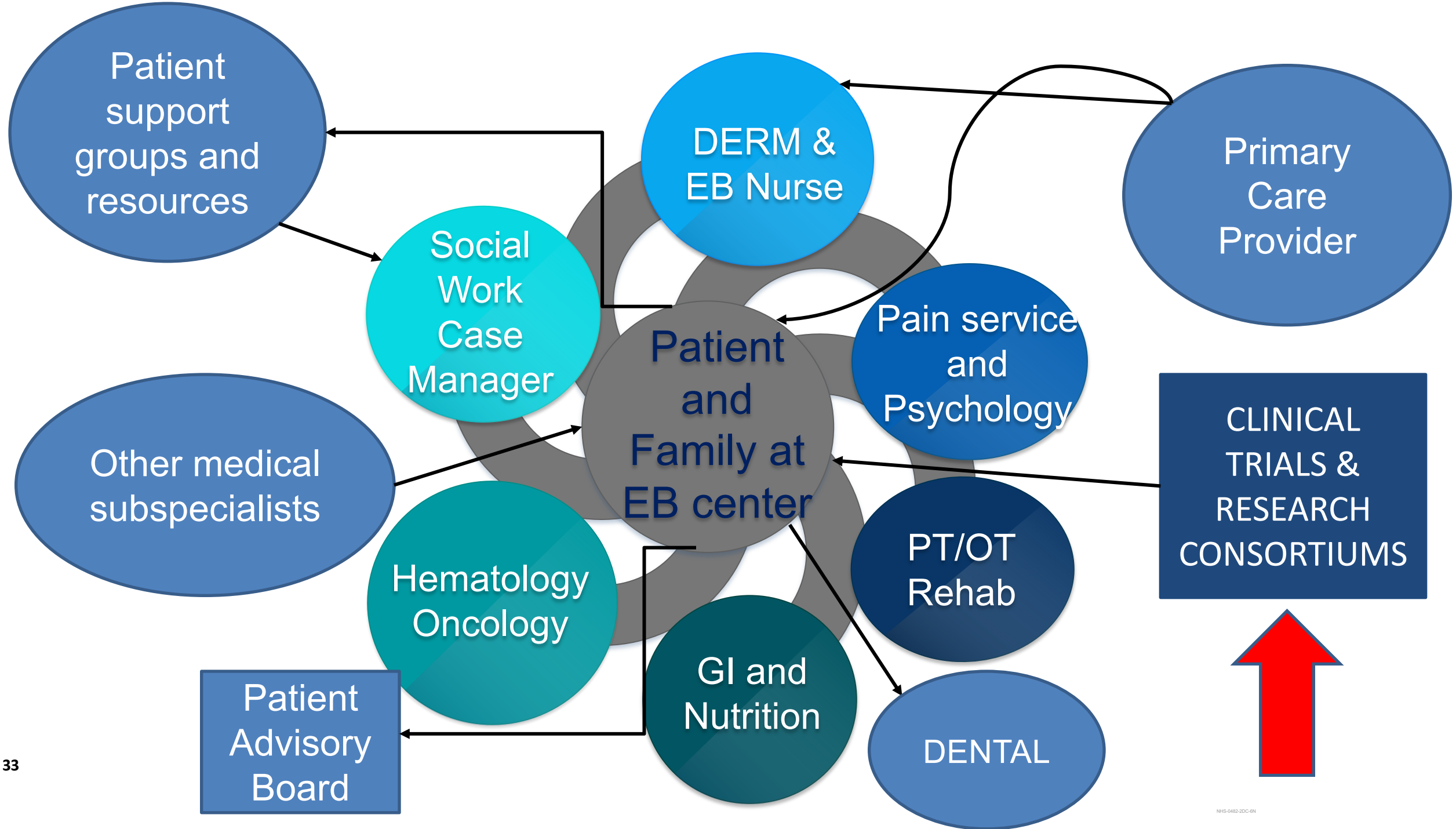

Patient support groups and resources
DERM & EB Nurse
Primary Care Provider
Social Work Case Manager
Patient and Family at EB center
Pain service and Psychology
Other medical subspecialists
CLINICAL TRIALS & RESEARCH CONSORTIUMS
Hematology Oncology
PT/OT Rehab
GI and Nutrition
Patient Advisory Board
DENTAL

Clinical trials in EB—local to broad effects

- Allogeneic cell therapies (keratinocytes, fibroblasts, stem cells)
- Hematopoietic stem cell transplant (BMT)
- Gene therapies--*ex vivo, in vivo*
- *Disease modifying, symptom relief therapies*
  - *Address the inflammatory and fibrotic processes*
- *Novel and re-purposed topical treatments*

ClinicalTrials.gov Search Results 09/07/2021

	Title	Status	Study Results	Conditions	Interventions	Locations
1	Improve Adherence to Weak or Strong Opioid Analgesics at the Time of Care in Children With Hereditary Epidermolysis Bullosa	Recruiting	No Results Available	•Epidermolysis Bullosa	•Other: Interview	•Hôpital Necker-Enfants Malades, Paris, France
2	The Natural History of Wounds in Patients With Dystrophic Epidermolysis Bullosa (DEB)	Recruiting	No Results Available	•Dystrophic Epidermolysis Bullosa •DEB - Dystrophic Epidermolysis Bullosa		•Stanford University, Redwood City, California, United States
3	Injections of Botulinic Toxin in Plantar Lesions of Localized Epidermolysis Bullosa Simplex	Recruiting	No Results Available	•Epidermolysis Bullosa Simplex	•Drug: Botulinic toxin •Drug: Placebo	•University Hospital Bordeaux, Bordeaux, France •University Hospital Nice, Nice, France •Saint-Louis Hospital - APHP, Paris, France •Hôpital Larrey - CHU Toulouse, Toulouse, France
4	Gynecological Follow-up of Patients With Dystrophic Epidermolysis Bullosa (EBD)	Recruiting	No Results Available	•Dystrophic Epidermolysis Bullosa	•Other: Decriptive study of EDB	•CHU de NICE, Nice, France •Hôpital Saint Louis, Paris, France
5	A Neurokinin-1 Receptor Antagonist for the Treatment of Pruritus in Patients With Epidermolysis Bullosa	Recruiting	No Results Available	•Epidermolysis Bullosa	•Drug: Serlopitant Tablet •Drug: Placebo Oral Tablet	•Stanford University, Redwood City, California, United States
6	Phase 3, Open-label Clinical Trial of EB-101 for the Treatment of Recessive Dystrophic Epidermolysis Bullosa (RDEB)	Recruiting	No Results Available	•Epidermolysis Bullosa •Recessive Dystrophic Epidermolysis Bullosa	•Biological: EB-101	•Stanford University, Redwood City, California, United States
7	A Study of FCX-007 for Recessive Dystrophic Epidermolysis Bullosa	Recruiting	No Results Available	•Recessive Dystrophic Epidermolysis Bullosa	•Biological: FCX-007 (dabocemagene autoficel; see below for FCX-007 description)	•Stanford University, Stanford, California, United States •Children's Hospital Colorado, Aurora, Colorado, United States •Solutions Through Advanced Research, Inc., Jacksonville, Florida, United States •Mayo Clinic, Rochester, Minnesota, United States •Dell Children's Medical Group, Austin, Texas, United States
8	Rigosertib in Patients With Recessive Dystrophic Epidermolysis Bullosa Associated SCC	Recruiting	No Results Available	•Recessive Dystrophic Epidermolysis Bullosa	•Drug: Rigosertib Sodium •Other: Quality-of-Life Assessment	•Sidney Kimmel Cancer Center at Thomas Jefferson Universit Philadelphia, Pennsylvania, United States
9	Characteristics of Patients With Recessive Dystrophic Epidermolysis Bullosa	Recruiting	No Results Available	•Epidermolysis Bullosa Dystrophica		•Stanford University School of Medicine, Stanford, California, United States
10	A Pilot Study to Explore the Role of Gut Flora in Epidermolysis Bullosa	Recruiting	No Results Available	•Epidermolysis Bullosa •Epidermolysis Bullosa Simplex •Epidermolysis Bullosa Dystrophica	•Other: No intervention	•ProgenaBiome, Ventura, California, United States
11	Topical Gentamicin Nonsense Suppression Therapy of EB	Recruiting	No Results Available	•Epidermolysis Bullosa	•Drug: Gentamicin Sulfate	•Oslo University Hospital, Oslo, Norway
12	Gentamicin for Junctional Epidermolysis Bullosa	Recruiting	No Results Available	•Junctional Epidermolysis Bullosa	•Drug: Gentamicin Sulfate	•University of Southern California, Los Angeles, California, United States
13	Study of Cellutome System for Treatment of Individual Lesions in EB Pts	Recruiting	No Results Available	•Epidermolysis Bullosa	•Device: Cellutome Epidermal Harvesting System	•University of Minnesota Masonic Cancer Center and Medical Center, Minneapolis, Minnesota, United States
14	MT2015-20: Biochemical Correction of Severe EB by Allo HSCT and Serial Donor MSCs	Recruiting	No Results Available	•Epidermolysis Bullosa	•Drug: Thymoglobulin •Drug: Cyclophosphamide •Drug: Fludarabine •Radiation: Total Body Irradiation •Procedure: Bone marrow infusion •Drug: Tacrolimus •Drug: Mycophenolate Mofetil •Biological: Donor mesenchymal stem cell infusions •Drug: Busulfan	•University of Minnesota Masonic Cancer Center and Medical Center, Minneapolis, Minnesota, United States
15	Intravenous Gentamicin Therapy for Recessive Dystrophic Epidermolysis Bullosa (RDEB)	Recruiting	No Results Available	•Recessive Dystrophic Epidermolysis Bullosa	•Drug: Gentamicin	•University of Southern California, Los Angeles, California, United States
16	Biochemical Correction of Severe EB by Allo HSCT and "Off-the-shelf" MSCs	Recruiting	No Results Available	•Epidermolysis Bullosa	•Drug: Cyclophosphamide •Drug: Fludarabine •Drug: Anti-thymocyte globulin •Drug: Cyclosporine A •Drug: Mycophenolate mofetil •Procedure: Mesenchymal stem cell transplantation •Radiation: Total body irradiation •Procedure: Bone marrow or umbilical cord blood (UCG) stem cell transplantation	•University of Minnesota Masonic Cancer Center and Medical Center, Minneapolis, Minnesota, United States
17	Optimizing IV Gentamicin in JEB	Recruiting	No Results Available	•Junctional Epidermolysis Bullosa	•Drug: Gentamicin Sulfate, Injectable	•University of Southern California, Los Angeles, California, United States
18	A Long-term Treatment With B-VEC for Dystrophic Epidermolysis Bullosa	Recruiting	No Results Available	•Dystrophic Epidermolysis Bullosa •DEB - Dystrophic Epidermolysis Bullosa •Recessive Dystrophic Epidermolysis Bullosa •Dominant Dystrophic Epidermolysis Bullosa	•Biological: Open Label Topical Beremagene Geperpavec (B-VEC)	•Mission Dermatology Center, Rancho Santa Margarita, California, United States •Stanford University, Redwood City, California, United States •Pediatric Skin Research, Coral Gables, Florida, United States •Northwestern University, Chicago, Illinois, United States •Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States •Ascension Seton- Dell's Children Medical Group, Austin, Texas, United States
19	Ex Vivo Gene Therapy Clinical Trial for RDEB Using Genetically Corrected Autologous Skin Equivalent Grafts	Enrolling by invitation	No Results Available	•Epidermolysis Bullosa Dystrophica, Recessive	•Biological: COL7A1-SIN retroviral vector engineered autologous tissue-engineered skin	•Institut Imagine Necker Hospital, Paris, France
20	Rigosertib for RDEB-SCC	Recruiting	No Results Available	•Epidermolysis Bullosa Dystrophica •Squamous Cell Carcinoma	•Drug: Rigosertib Oral Capsules / Rigosertib Intravenous	•EB House Austria/Dept. of Dermatology University Hospital, Salzburg, Austria
21	Pregabalin Treatment for RDEB Pain and Itch	Recruiting	No Results Available	•Pain, Neuropathic •Itch •Epidermolysis Bullosa	•Drug: Pregabalin	•The Hospital for Sick Children, Toronto, Ontario, Canada
22	Long-Term Follow-up Protocol	Recruiting	No Results Available	•Dystrophic Epidermolysis Bullosa •Recessive Dystrophic Epidermolysis Bullosa •Dominant Dystrophic Epidermolysis Bullosa		•Mission Dermatology Center, Rancho Santa Margarita, California, United States •Stanford University, Redwood City, California, United States •Pediatric Skin Research, Coral Gables, Florida, United States

clinicaltrials.gov, 23 interventional studies*

**Recruiting, Enrolling by invitation*

PHOENIX CHILDREN'S Hospital

ClinicalTrials.gov Search Results 09/07/2021

	Title	Status	Study Results	Conditions	Interventions	Locations
1	Self-Assembled Skin Substitute for the Treatment of Epidermolysis Bullosa	Active, not recruiting	No Results Available	• Epidermolysis Bullosa Dystrophica	• Biological: SASS	• The Hospital for Sick Children, Toronto, Ontario, Canada
2	Phase III Efficacy and Safety Study of Oleogel-S10 in Epidermolysis Bullosa	Active, not recruiting	No Results Available	• Epidermolysis Bullosa	• Drug: Oleogel-S10 • Drug: Placebo	• Phoenix Children's Hospital, Phoenix, Arizona, United States • Children's Hospital Colorado, Aurora, Colorado, United States • Amjad Plastic Research, Miami, Florida, United States • University of Minnesota, Minneapolis, Minnesota, United States • Stony Brook University Hospital, Stony Brook, New York, United States • Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States • The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States • Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, United States • Medical University of South Carolina, Charleston, South Carolina, United States • Texas Dermatology and Laser Specialists, San Antonio, Texas, United States • and 41 more
3	Allogeneic ABCB5-positive Stem Cells for Treatment of Epidermolysis Bullosa	Active, not recruiting	No Results Available	• Recessive Dystrophic Epidermolysis Bullosa	• Biological: allo-APZ2-EB	• University of Minnesota, Masonic Cancer Center and Medical Center, Minneapolis, Minnesota, United States • EB-Haus Austria; Salzburger Landeskliniken (SALK); Paracelsus Medizinische Privatuniversität Salzburg (PMU), Salzburg, Austria • Hôpital Saint-Louis; Département de dermatologie, Paris, France • Department of Dermatology, Medical Center-University of Freiburg, Freiburg, Germany • King's College London; St John's Institute of Dermatology;, London, United Kingdom • Great Ormond Street Hospital; Dermatology Department, London, United Kingdom
4	A Study of PTR-01 in Recessive Dystrophic Epidermolysis Bullosa	Active, not recruiting	No Results Available	• Recessive Dystrophic Epidermolysis Bullosa	• Drug: PTR-01	• Stanford University, Redwood City, California, United States • Children's Hospital Colorado, Aurora, Colorado, United States
5	Topical Beremagene Geperpavec (KB103) Gene Therapy to Restore Functional Collagen VII for the Treatment of Dystrophic Epidermolysis Bullosa	Active, not recruiting	No Results Available	• Dystrophic Epidermolysis Bullosa	• Biological: Topical beremagene geperpavec	• Stanford University, Stanford, California, United States
6	A Study of FCX-007 for Recessive Dystrophic Epidermolysis Bullosa (RDEB)	Active, not recruiting	No Results Available	• Epidermolysis Bullosa Dystrophica, Recessive	• Genetic: FCX-007	• Stanford University, Stanford, California, United States • Children's Hospital Colorado, Aurora, Colorado, United States
7	Gene Transfer for Recessive Dystrophic Epidermolysis Bullosa	Active, not recruiting	No Results Available	• Epidermolysis Bullosa Dystrophica • Epidermolysis Bullosa	• Biological: LZRSE-Col7A1 Engineered Autologous Epidermal Sheets	• Stanford University School of Medicine, Stanford, California, United States
8	The Objective of This Study is to Compare the Efficacy and Safety of Beremagene Geperpavec (B-VEC) Topical Gel With That of Placebo for the Treatment of Dystrophic Epidermolysis Bullosa (DEB).	Active, not recruiting	No Results Available	• Dystrophic Epidermolysis Bullosa • Recessive Dystrophic Epidermolysis Bullosa • Dominant Dystrophic Epidermolysis Bullosa	• Biological: Topical Beremagene Geperpavec • Other: Placebo	• Mission Dermatology Center, Rancho Santa Margarita, California, United States • Stanford University, Stanford, California, United States • Pediatric Skin Research, LLC, Coral Gables, Florida, United States

	Title	Status	Study Results	Conditions	Interventions	Locations
9	Clinical Trial to Assess Safety and Efficacy of Autologous Cultured Epidermal Grafts Containing Epidermal Stem Cells Genetically Modified in Patients With JEB (HOLOGENE17)	Active, not recruiting	No Results Available	• Junctional Epidermolysis Bullosa	• Other: Transplantation surgery of genetically corrected cultured epidermal autograft (ATMP)	• EB House Austria, Department of Dermatology, Paracelsus Medical University, Salzburg, Austria
10	Clinical Trial to Assess Safety and Efficacy of Autologous Cultured Epidermal Grafts Containing Epidermal Stem Cells Genetically Modified in Patients With RDEB.	Active, not recruiting	No Results Available	• Recessive Dystrophic Epidermolysis Bullosa	• Drug: Genetically corrected cultured epidermal autograft (ATMP)	• EB House Austria, Department of Dermatology, Paracelsus Medical University, Salzburg, Austria
11	The State of Sexual Development in Children With Inherited Epidermolysis Bullosa	Active, not recruiting	No Results Available	• Dermatologic Disease • Epidermolysis Bullosa • Epidermolysis Bullosa Simplex • Epidermolysis Bullosa Dystrophica • Epidermolysis Bullosa, Junctional • Kindler Syndrome • Puberty Disorders • Hormone Disturbance	• Diagnostic Test: Biochemical study of hormone levels • Diagnostic Test: Ultrasound examination • Radiation: Radiography of the hands • Behavioral: Consultation of a medical psychologist	• National Medical Research Center for Children's Health, Moscow, Russian Federation
12	Using Topical Sirolimus 2% for Patients With Epidermolysis Bullous Simplex (EBS) Study	Active, not recruiting	Has Results	• Epidermolysis Bullosa Simplex • Epidermolysis Bullosa Simplex Kobner • Weber-Cockayne Syndrome	• Drug: Sirolimus, 2% • Drug: Vehicle	• Stanford University, Palo Alto, California, United States
13	Computational Drug Repurposing for All EBS Cases	Active, not recruiting	No Results Available	• Epidermolysis Bullosa • Healthy • Genetic Skin Disease • Epidermolysis Bullosa Simplex • Epidermolysis Bullosa, Junctional • Epidermolysis Bullosa Dystrophica	• Procedure: Experimental Group	• Pediatric Dermatology Clinic at Stanford Children's Hospital, Palo Alto, California, United States

clinicaltrials.gov, 13 active, not recruiting

How can clinical trials in EB potentially improve the patient's disease burden?

- Clarify or confirm genetic diagnosis if testing is provided
- More frequent visits and provider contact
- No/less discrimination based on insurance, SES, location
- Potential for short term relief from itch, pain, wound burden
- Potential for long term open label access to drug

Lessons learned from an EB PI

- Patients (subjects) are often desperate to try anything
- Deviation from typical wound care or increase burden of wound care at home is a ***barrier and burden***
- ***Wounds are dynamic, lots of factors to consider***
- ***Patient reported outcomes (QOL, itch, pain, etc) are critical***
- Beware of exhausting your own study populations

Thank You

hprice@phoenixchildrens.com

EPIDERMOLYSIS BULLOSA CLINICAL RESEARCH CONSORTIUM (EBCRC)

OLEOGEL-S10 UPDATE

DR. TRACY CUNNINGHAM, VP, HEAD OF DEVELOPMENT

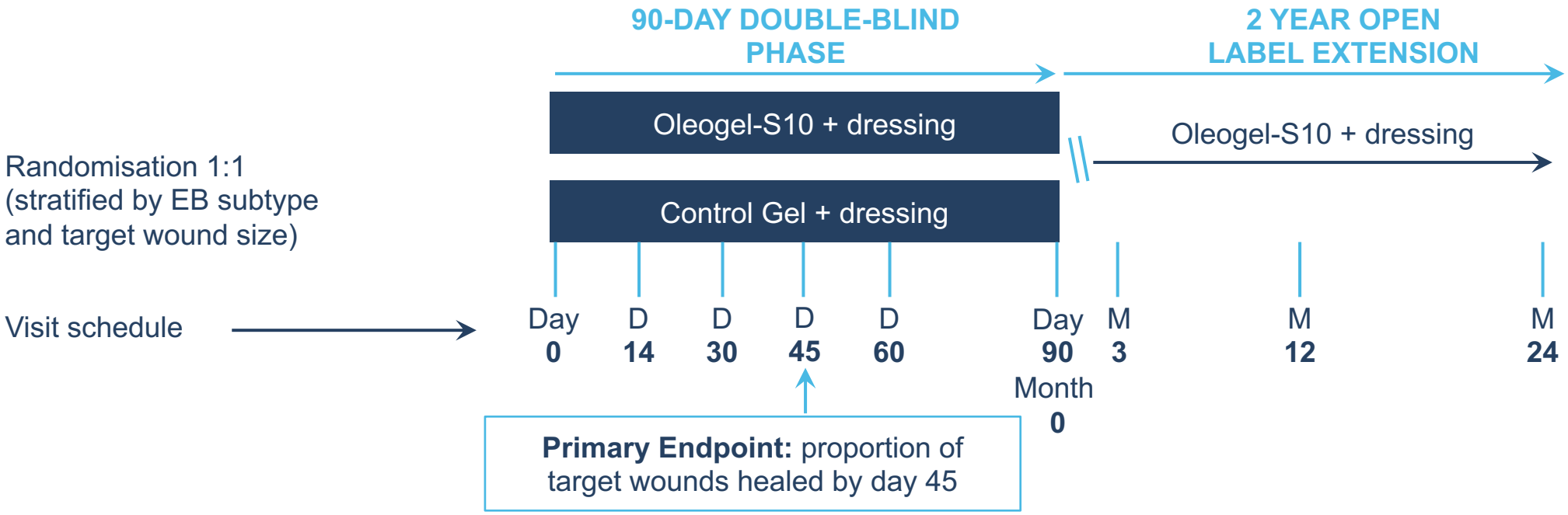
SHEILA FRAME, PRESIDENT, AMERICAS

OLEOGEL-S10 EASE PHASE 3 STUDY IN EB

✓ **Primary endpoint met, September 2020**

✓ **p-value = 0.013**

LARGEST EVER GLOBAL PHASE 3 STUDY IN EB



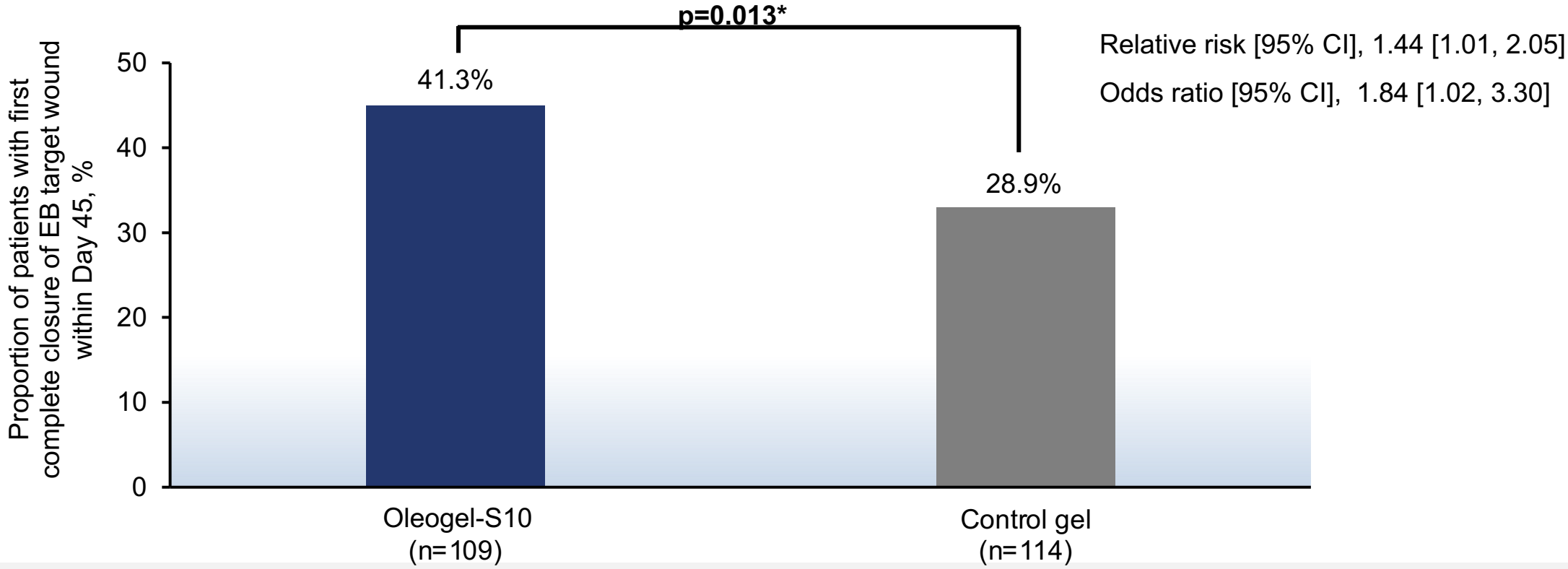
DOUBLE BLIND, RANDOMIZED, PLACEBO CONTROLLED, PHASE 3, EFFICACY AND SAFETY STUDY OF OLEOGEL-S10 IN PATIENTS WITH JUNCTIONAL AND DYSTROPHIC EB

Oleogel-S10 (Filsuvez®) is an investigational product for the treatment of EB

OLEOGEL-S10 - POTENTIAL FIRST IN MARKET THERAPY FOR EB

- Phase 3 EASE study investigating Oleogel-S10 was the largest ever global trial and first ever positive readout in EB
- Primary endpoint was met demonstrating 44% increase in target wound closure with Oleogel-S10 versus control gel
- Favorable trends observed among secondary endpoints including procedural pain, change in EBDASI score and BSAP
- Oleogel-S10 was shown to have an acceptable safety profile

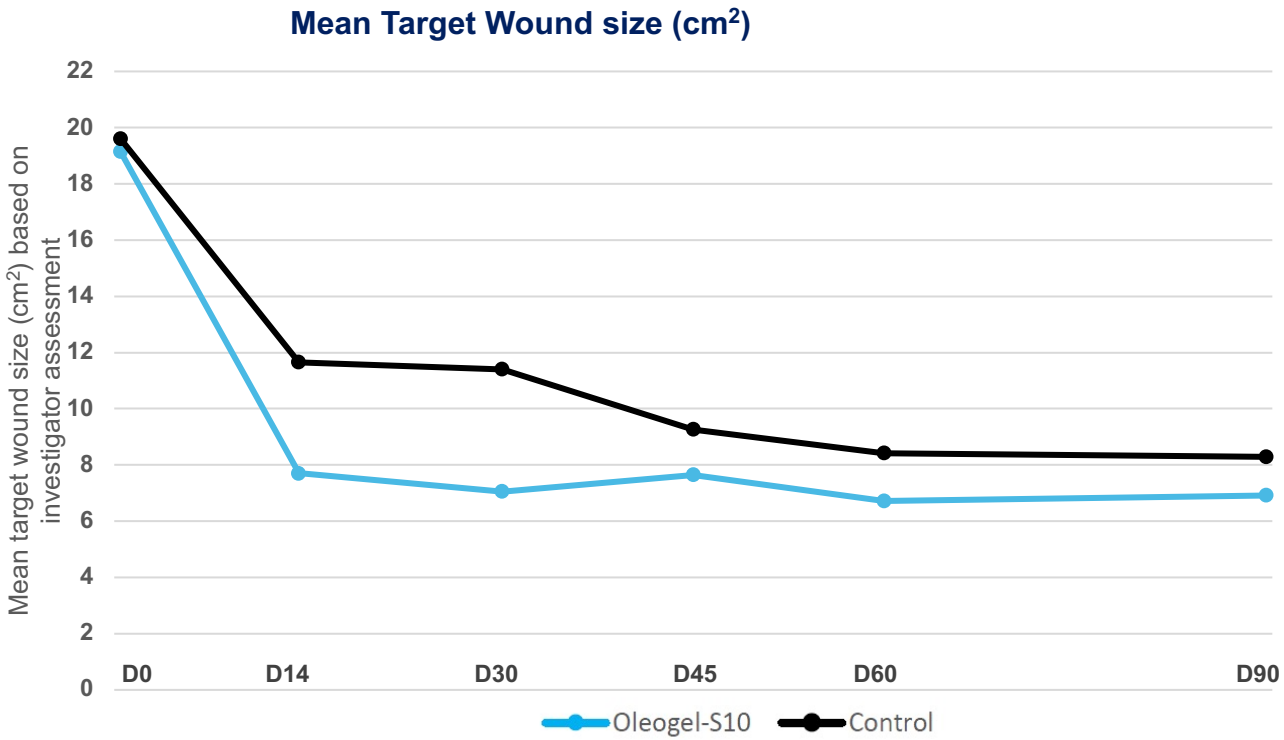
Proportion of patients with first complete target wound closure within Day 45

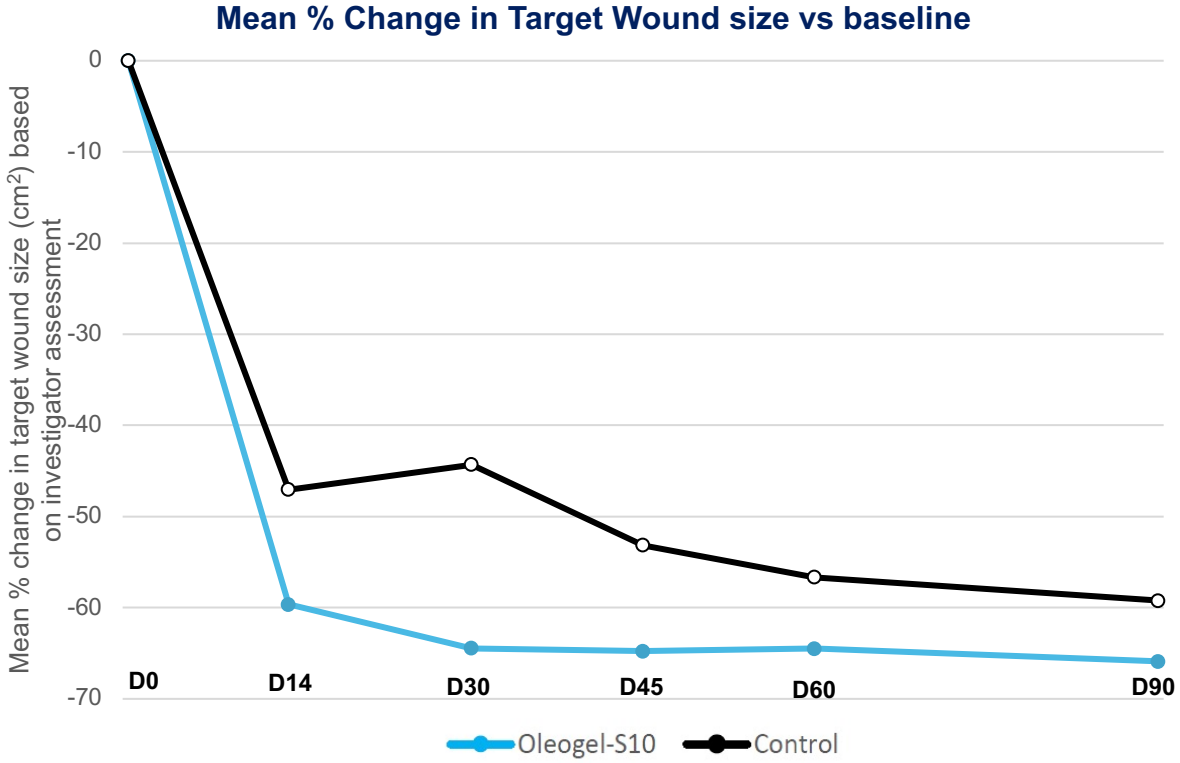


* Pre-specified adjustment to account for IDMC interim sample size re-estimation
CI, confidence interval

AMRYT PHARMA

OLEOGEL-S10 – PHASE 3 EASE: REDUCTION IN TARGET WOUND SURFACE AREA





Oleogel-S10 (all patients): 65.9% reduction in mean surface area over 90 days treatment

- Substantial early reduction from day 14 which was then maintained

No. Patients	Day 0	Day 14	Day 30	Day 45	Day 60	Day 90
Oleogel-S10	107	102	98	87	91	79
Control gel	111	107	101	97	95	84

Evaluation of target wound size by investigator assessment

OLEOGEL-S10 – PHASE 3 EASE: TIME TO FIRST COMPLETE CLOSURE OF EB TARGET WOUND WITHIN D90 – BY EB SUBTYPE

	RDEB		DDEB		JEB	
	Oleogel-S10 (N=91)	Control Gel (N=84)	Oleogel-S10 (N=6)	Control Gel (N=14)	Oleogel-S10 (N=11)	Control Gel (N=15)
Closure	**52.7%**	**44.0%**	**66.7%**	**57.1%**	**18.2%**	**33.3%**
Time to first complete closure (days) Mean (SD)	**37.9** (20.76)	**46.9** (27.31)	**28.8** (19.75)	**31.0** (14.68)	**24.0** (15.56)	**48.0** (29.18)
95% CI Mean	(31.9, 44.0)	(37.8, 56.1)	(-2.7, 60.2)	(18.7, 43.3)	(-115.8, 163.8)	(11.8, 84.2)
Minimum - maximum	14 - 95	15 - 96	10 - 56	15 - 58	13 - 35	15 - 94
Median	33.5	45.0	24.5	29.5	24.0	47.0
Log-rank Test						
p-value	0.175		0.890		0.382	

OLEOGEL-S10 - US & EUROPEAN ANTICIPATED REGULATORY TIMELINES

NDA TIMELINE – FDA – 6 MONTH PRIORITY REVIEW AND ROLLING NDA

2020

January — **December**

- **Apr** - Type C meeting completed
- **Jun** - Module 3 CMC request for priority review submitted
- **Sept** – Positive Top Line Phase 3 Results w/ primary endpoint met
- **Dec**- pre-NDA meeting

2021

January — **December**

- **Mar** - Initial submission
- **Jun -** NDA accepted; Priority review granted and PDUFA date set for Nov 30, 2021
- **From July –** Info. request submission of responses on time
- **Nov** - Anticipated Approval Date
- **Nov** - Priority Review Voucher

MAA TIMELINE – EMA

2020

January — **December**

- **Jun** – MAA Letter of Intent submitted to EMA
- **Sep** – Rapporteurs assigned by CHMP
- **Nov** – MAA Pre-submission meetings

2021

January — **December**

- **Mar** - Initial submission
- **Jul** - List of Questions (LoQ) received
- **Sep** - Submission of responses to LoQ (D120) – On Track
- **Nov** - List of Outstanding Issues (LoOI) received and responses submitted
- **Dec** - CHMP Opinion

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POTENTIAL FIRST AND ONLY APPROVED PRODUCT TO TREAT EB

78 DAYS TO PDUFA – THE MARKET IS READY….AND SO ARE WE

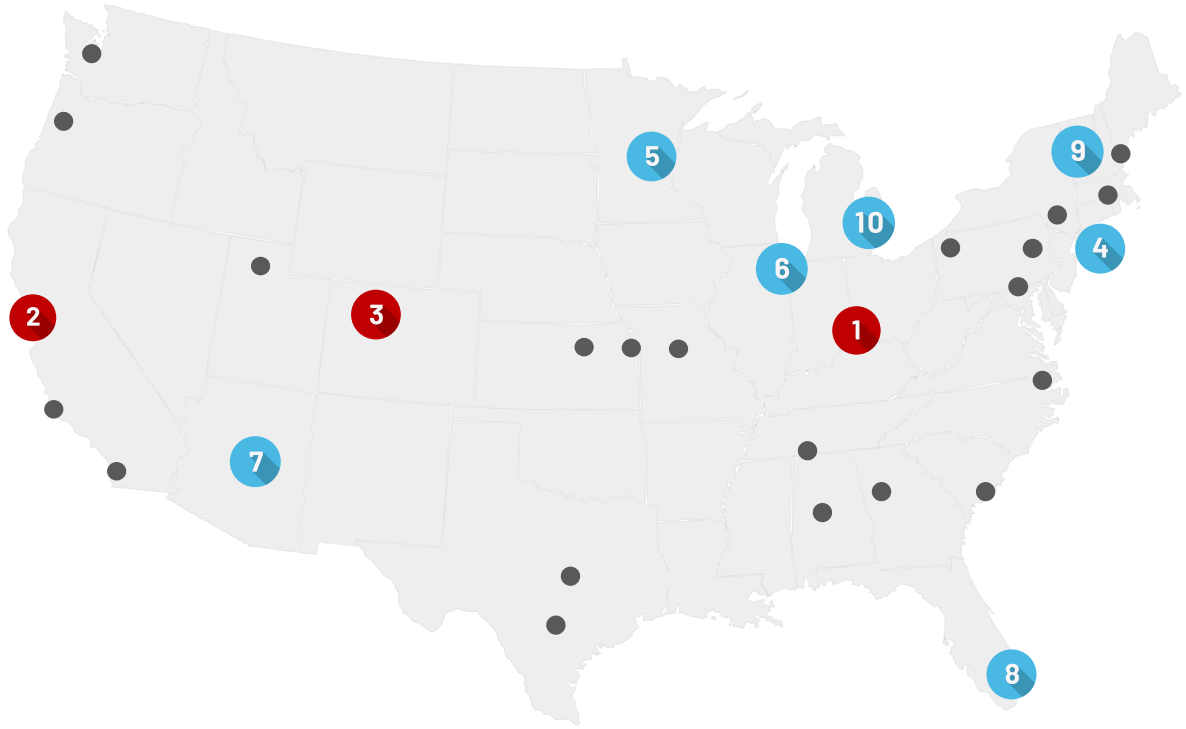
"I believe, and I know in my heart of hearts, that we will have at least one approved drug to treat EB by next Father's Day."
Brett Kopelan, Executive of Debra of America

"A big step in the right direction!"
Michael P. Hund
Chief Executive Officer, EB Research Partnership

Oleogel-S10 (Filsuvez®) is an investigational product for the treatment of EB

AMRYT PHARMA

TEN CENTERS IN THE US APPEAR TO HAVE THE MAJORITY OF SEVERE EB PATIENTS



1 2 3 National centers

4 5 6 7 8 9 10 Major centers with EB clinic

● Minor centers with strong pediatric dermatology, also seeing adults

Cincinnati CH is the largest EB center in the US with 150 patients but is strictly pediatric; Stanford is the only hospital with a dedicated adult EB clinic in addition to a pediatric clinic

Key centers

National centers of reference for Debra

1. Cincinnati CH / Univ. of Ohio*
2. Stanford CH*
3. Colorado CH / Univ. of Colorado
4. Morgan Stanley CH / Columbia Univ.
5. Univ. of Minnesota Masonic CH
6. Lurie CH / Northwestern Univ.
7. Phoenix CH / Univ. of Arizona.
8. Jackson Memorial Hospital / Univ. of Miami
9. Univ. of Massachusetts Memorial CH
10. Henry Ford Hospital

● Other centers treating EB patients

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AMRYT TAKES A BROAD, PATIENT-CENTRIC APPROACH

Access to Products

Prior authorizations are anticipated. Product is ready and pre-filled in tubes. Specialty Pharmacy is ready for packaging and early distribution.

Centralised Treatment Centres

3 key centres and 7 regional centres in the US facilitates commercialization.

Educational Need

Need to educate non-EB specialists in the community ensuring patients can access the product easily.

Specialist Nurses

EB wound clinic nurses/wound nurses in community are key and often provide guidance/training on therapeutic options.

Homecare

Homecare is highly valued however is not very accessible to the majority of families.

MAKING OLEOGEL-S10 THE BACKBONE OF TREATMENT IN SEVERE EB*

Preparing for Launch

- Dedicated expert medical affairs team in field
- Early payer engagement
- Dedicated dermatology commercial team trained for day 1 launch
- Exceptional patient support services
- Easy to use and ready for distribution directly to patients to have on hand day 1

*Seeking FDA approval for the indication of accelerated healing of wounds in adult and pediatric patients with dystrophic (DEB) and junctional epidermolysis bullosa (JEB), two of the most severe forms of EB.

78 DAYS TO TARGET PDUFA –THE MARKET IS READY…AND SO ARE WE

Oleogel-S10 demonstrated accelerated wound healing, with an acceptable safety profile, and conveniently fits into patients' daily routine at home.

- Commercial launch plans at advanced stage
- Dedicated medical affairs team in field
- Dedicated commercial team in recruitment

- Enthusiasm among the EB community
- Strong partnership with patient advocacy organizations
- Website launched: www.livingwitheb.com

- Engage payers to achieve early and sustainable patient access by minimizing access barriers
- Ensure seamless customer experience

50

DR. MARIA FLESERIU - ACROMEGALY DISCUSSION

DR. MARIA FLESERIU

Maria Fleseriu, MD, FACE is a Professor of Medicine and Neurological Surgery and Director of the Pituitary Center at Oregon Health and Science University in Portland, Oregon, USA and Past President of the Pituitary Society. Dr. Fleseriu has a long-standing clinical and research interest in the pathophysiology and treatment of pituitary and adrenal disorders and has been global principal investigator in many pituitary clinical trials. She is a frequent plenary guest speaker at national and international meetings and has authored over 200 manuscripts, including guidelines, consensus papers and book chapters. Major focus on research now is individualized treatment of acromegaly and Cushing's. Dr. Fleseriu has been awarded the title of "Doctor Honors Causa" by the University of Medicine and Pharmacy "Carol Davila" Bucharest, she serves on the Board of Directors for Pituitary Society as Program Chair and she is past chair of the Endocrine Society Guidelines Committee and the Hypopituitarism task force. She has also served on several committees for the Endocrine Society, Pituitary Society, European Society of Endocrinology and American Association of Clinical Endocrinology.

Dr. Fleseriu is Associate Editor for *European Journal of Endocrinology*, Chief Editor of Pituitary Endocrinology for *Frontiers in Endocrinology,* Section Head for *Pituitary and Neuroendocrine F 1000,* Associate Editor for *Reviews in Endocrinology* and *Metabolism,* Senior Editor *for Endocrinology, Diabetes and Metabolism CR* and a member of the editorial board of *Pituitary*. She has been involved in leadership positions of educational programs sponsored by the Endocrine Society, the Pituitary Society, and patient advocacy groups to teach physicians and patients about pituitary tumors and neuroendocrine disorders. She has served on multiple scientific advisory boards for biotechnology and pharmaceutical companies and participated in study design and has been global principal investigator for several Cushing's and acromegaly studies.

Acromegaly updates and Oral Octreotide Clinical Trials
(Focus on Chiasma OPTIMAL)

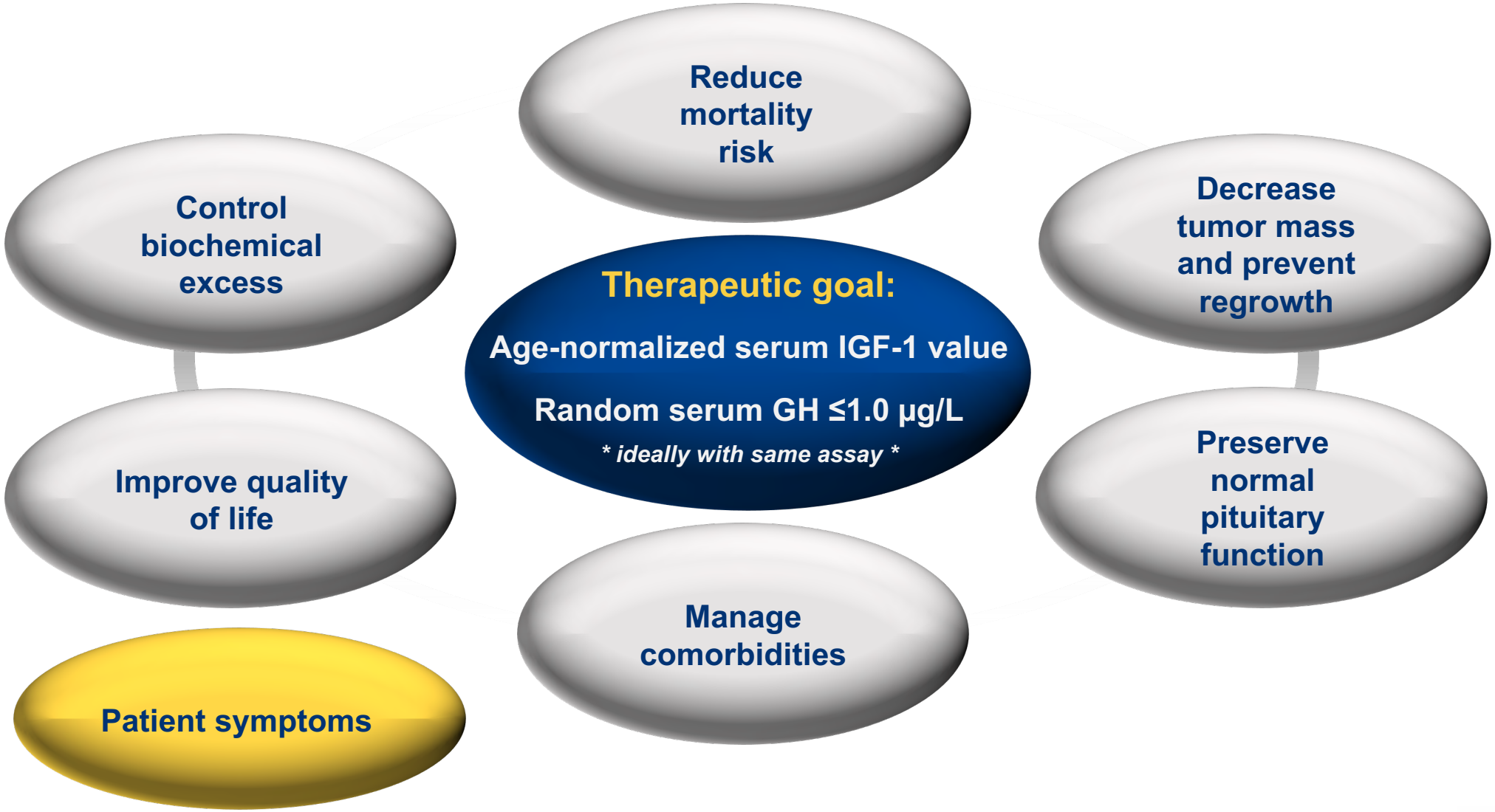
Maria Fleseriu, MD, FACE

Professor Medicine (Endocrinology) and Neurological Surgery

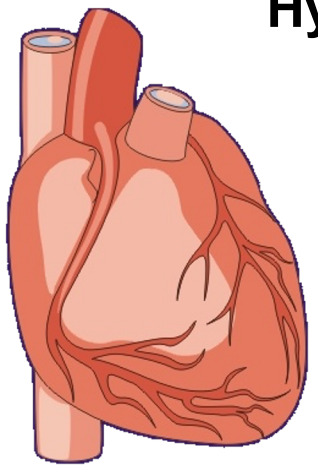
Director Pituitary Center

Oregon Health & Science University, Portland, OR

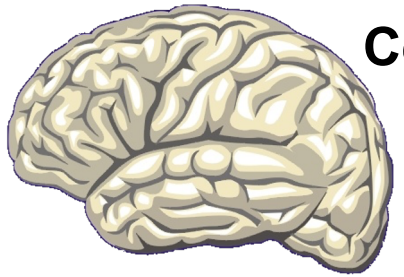
Optimal clinical outcomes in acromegaly



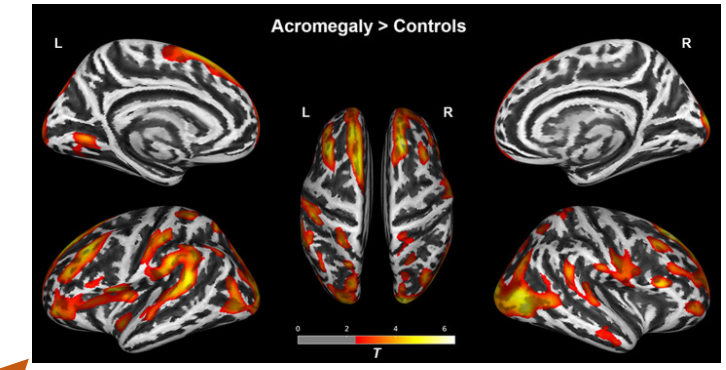
Katznelson L, et al. *J Clin Endocrinol Metab.* 2014; 99: 3933–51; Fleseriu M, et al. *Pituitary*. 2020. doi: 10.1007/s11102-020-01091-7



Hypertension and heart disease

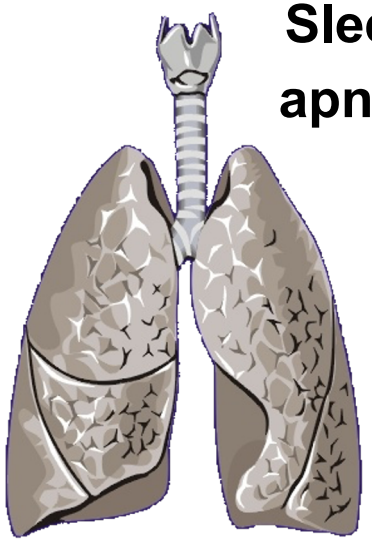


Cerebrovascular events
Headache

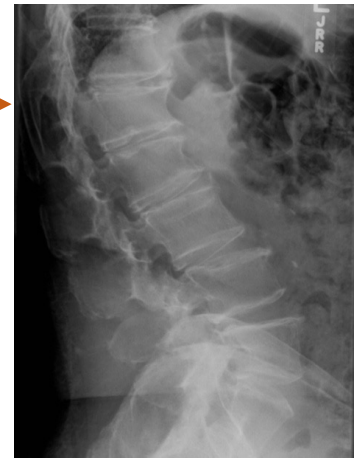


Increased cortical thickness
Neuropsychological dysfunction

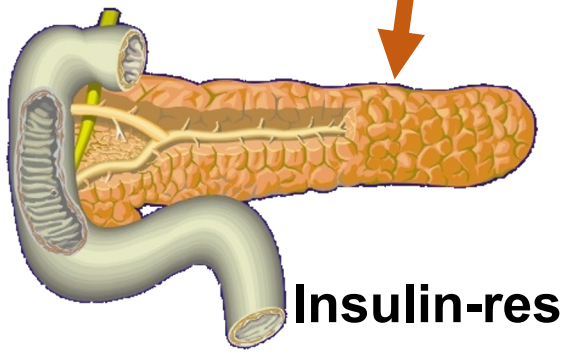
Acromegaly comorbidities



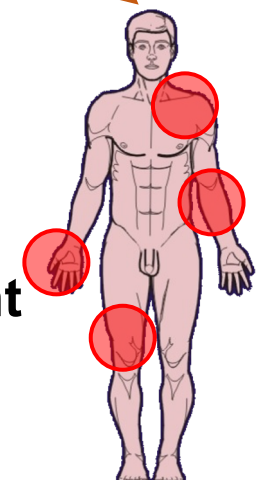
Sleep apnea



Vertebral Fractures
(*DEXA not reliable)*

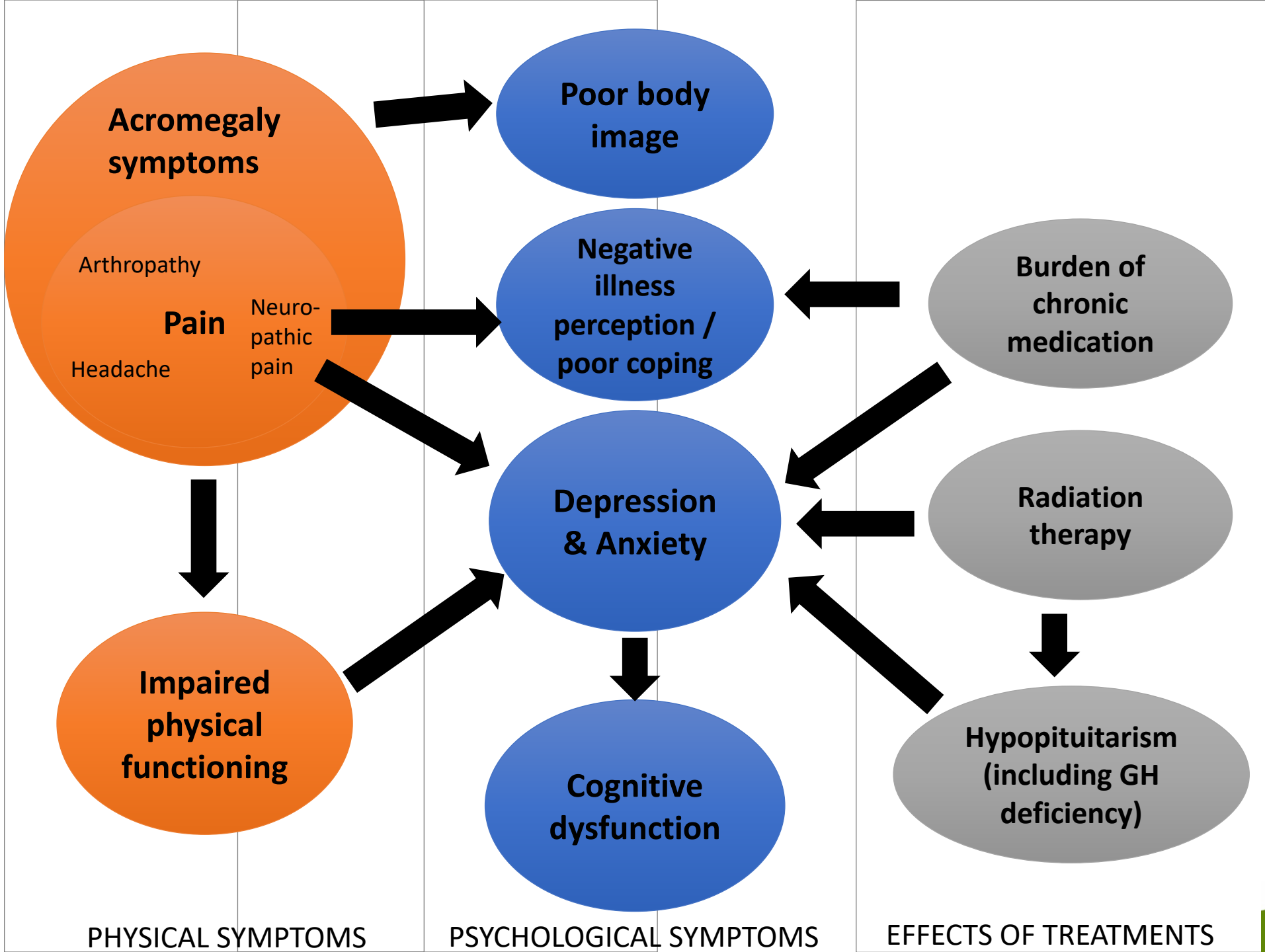


Insulin-resistant diabetes



Arthritis

Gadelha MR, et al. *Endocr Rev.* 2019;40(1):268-332. Yuan T et al, Front Oncology, 2021



Gadelha MR, et al. *Endocr Rev.* 2019;40(1): 268-332.

Medical therapies: How do we decide what to use and when?

Pituitary
https://doi.org/10.1007/s11102-020-01091-7

Check for updates

A Pituitary Society update to acromegaly management guidelines

Maria Fleseriu[1] · Beverly M. K. Biller[2] · Pamela U. Freda[3] · Monica R. Gadelha[4] · Andrea Giustina[5] · Laurence Katznelson[6] · Mark E. Molitch[7] · Susan L. Samson[8] · Christian J. Strasburger[9] · A. J. van der Lely[10] · Shlomo Melmed[11]

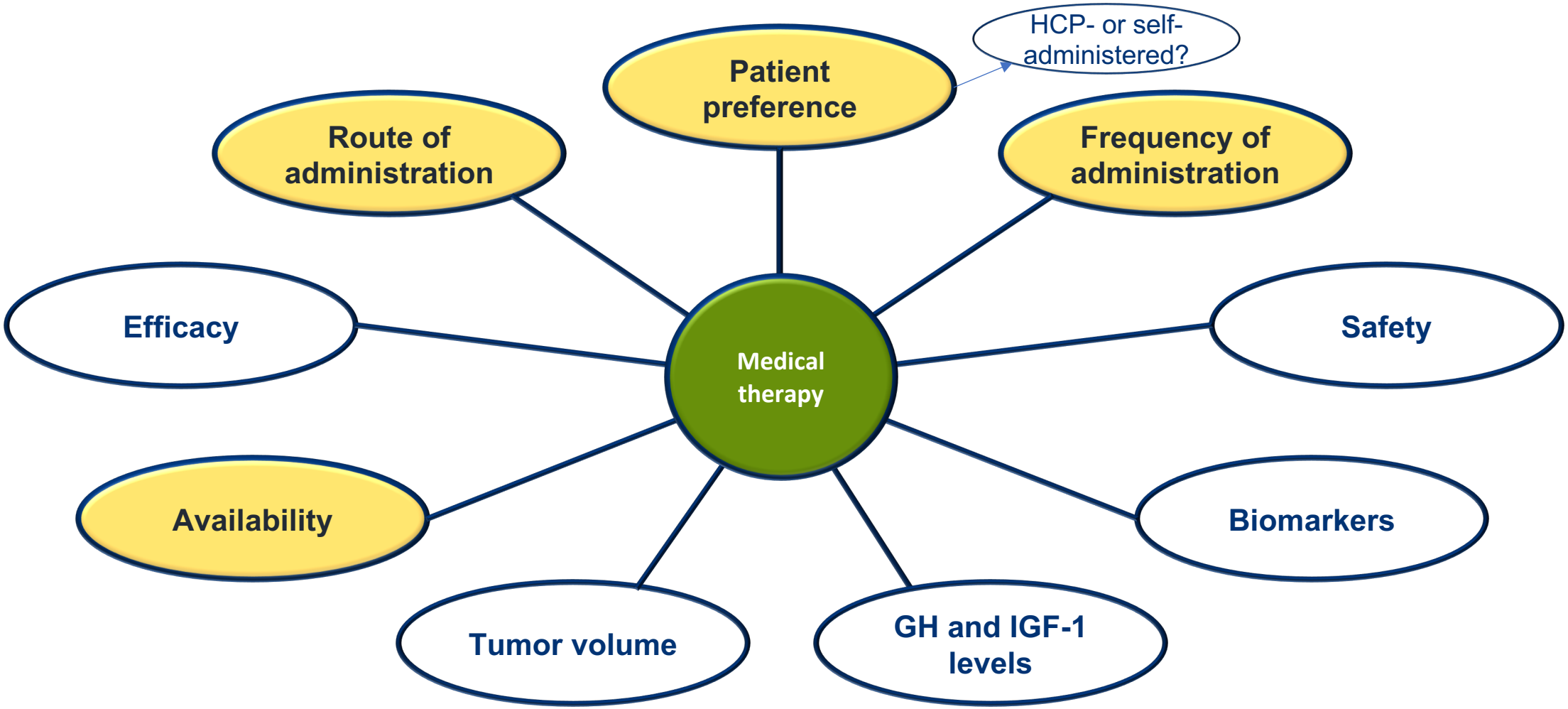
Accepted: 28 September 2020

Tumor volume

GH and IGF-1 levels

Giustina et al. *Rev Endocr Metab Disord.* 2020; 21: 667-78; Giustina, et al. *J Clin Endocrinol Metab.* 2020, 105(4): e937–46.

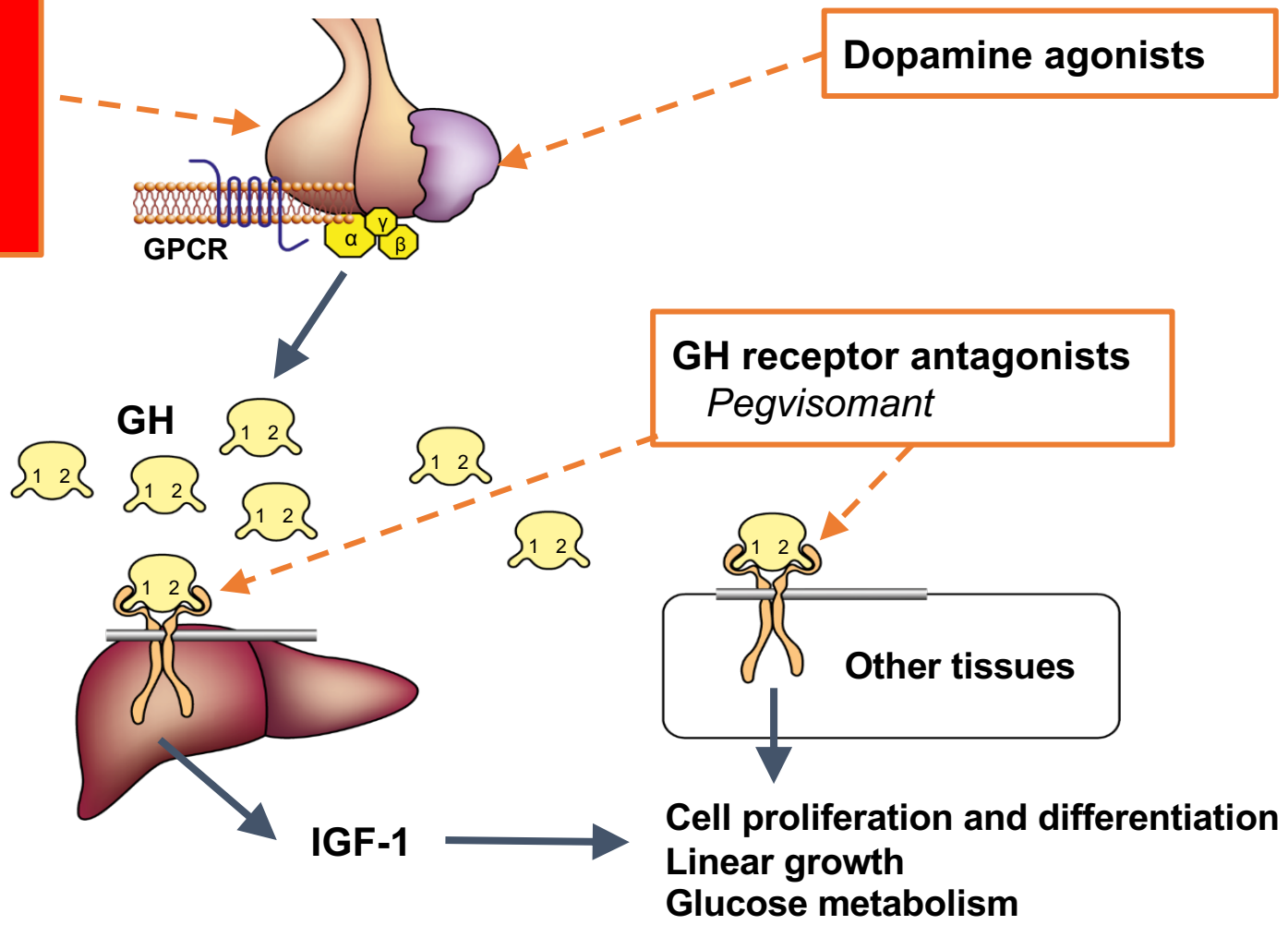
Medical therapies: How do we decide what to use and when?



Giustina et al. *Rev Endocr Metab Disord.* 2020; 21: 667-78; Giustina, et al. *J Clin Endocrinol Metab.* 2020, 105(4): e937–46.

Currently Available Medical Treatment Options

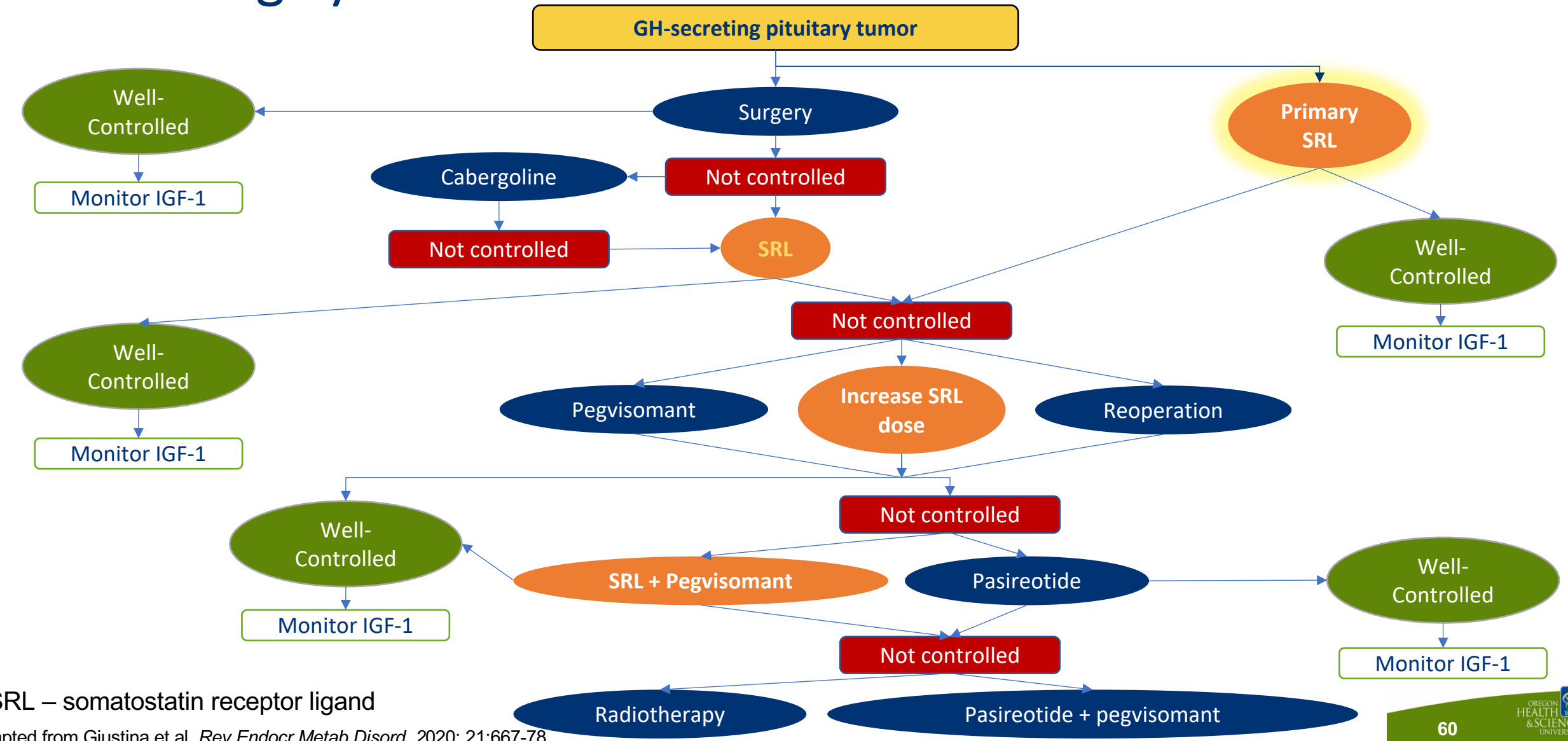
Somatostatin receptor ligands:
- *Octreotide LAR*
- *Lanreotide Autogel*
- *Oral Octreotide capsules*
- *Pasireotide LAR*



GPCR = G protein-coupled receptor; LAR = long-acting release.

Fleseriu M. *Discov Med.* 2014;17(96):329-338., Fleseriu M, et al. *Pituitary.* 2021;24(1):1-13.

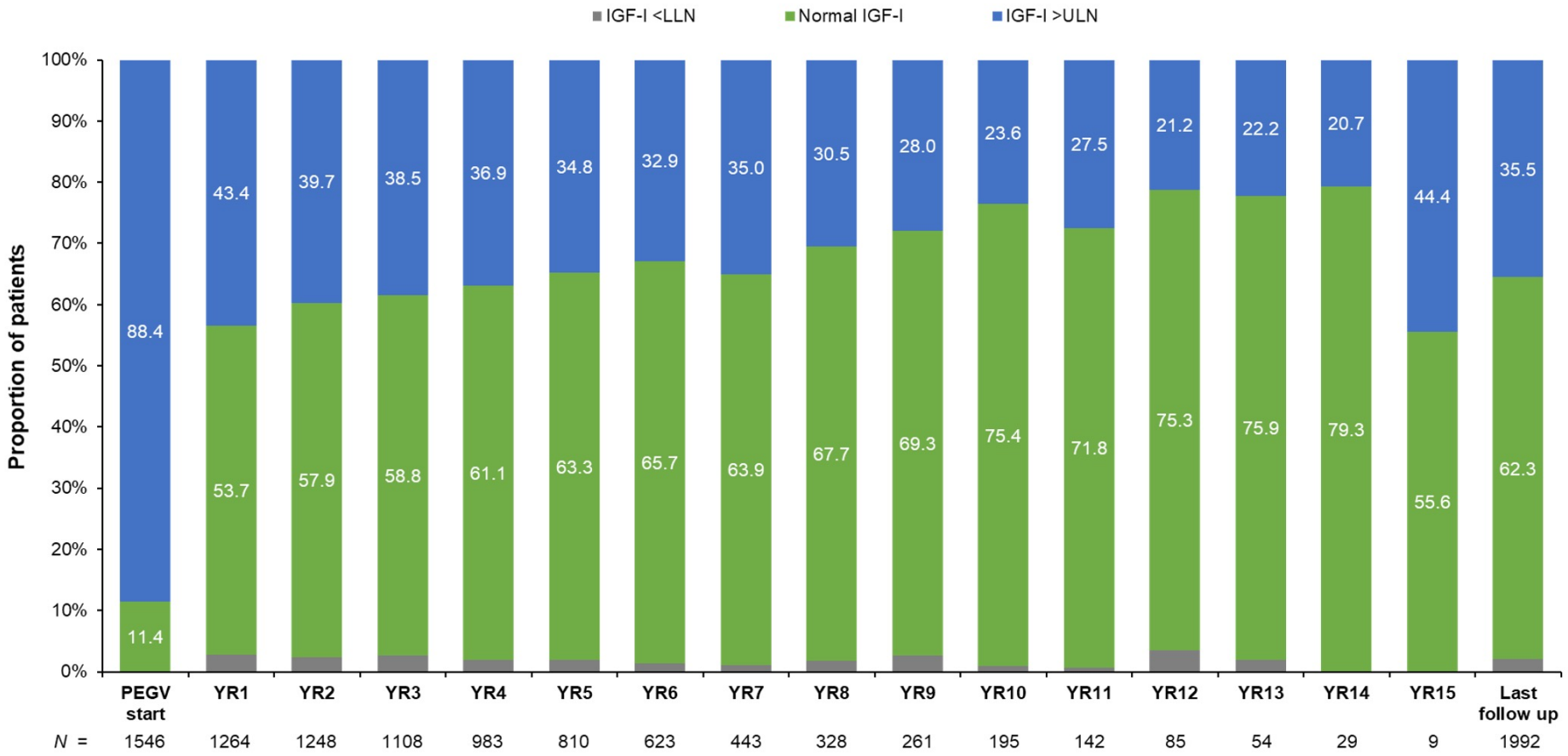
SRLs play an important role in multiple steps in the treatment of acromegaly



* SRL – somatostatin receptor ligand

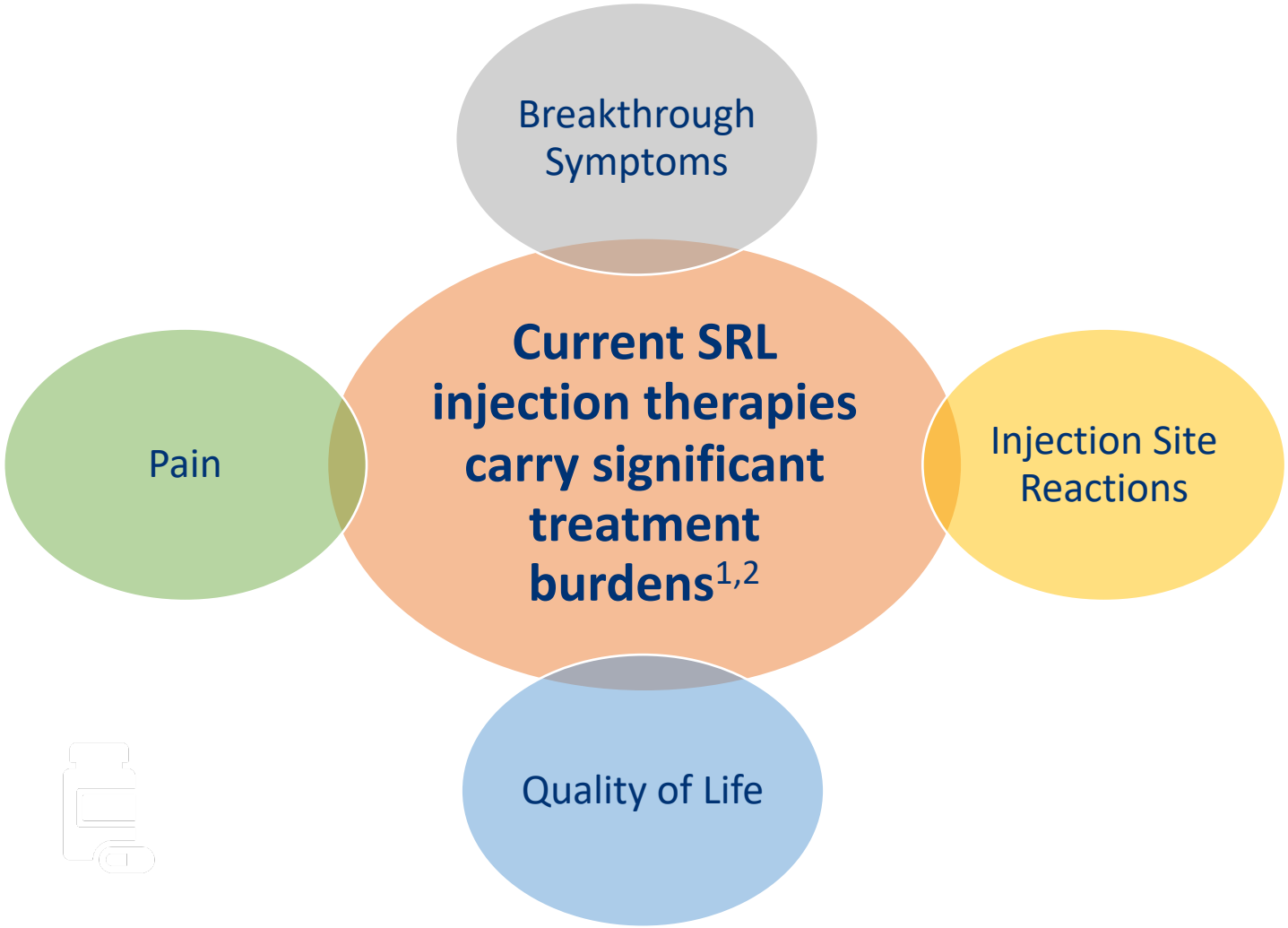
Adapted from Giustina et al. *Rev Endocr Metab Disord.* 2020; 21:667-78

Biochemical control in observational studies: ACROSTUDY



Fleseriu et al, European Journal of Endocrinology, 2021

Unmet need in the treatment of acromegaly



To provide a potential option that could address challenges with injections, Oral Octreotide Capsules (OOC) were developed

OOC, oral octreotide capsules.

1. Strasburger CJ, et al. *Eur J Endocrinol.* 2016;174(3):355-362. 2. Fleseriu M et al, *Pituitary* 2020, Aug;23(4):347-358.

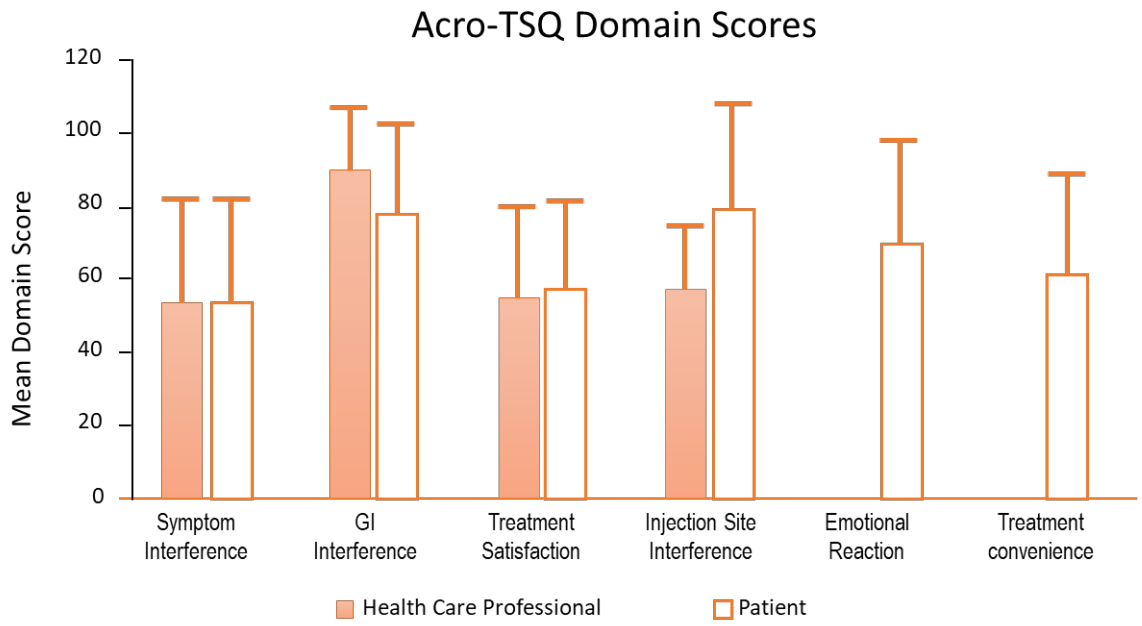
Concordance between patient-reported and HCP-reported treatment outcomes is low

Patients reported more:

- Headache
- Excess sweating
- Joint pain
- Carpal tunnel syndrome
- Vision problems
- Swelling
- Snoring
- Acro-fog

HCPs reported more:

- Fatigue
- Weakness
- Feeling tired



Geer E, et al. *Pituitary*. 2019; https//doi.org/10.1007/s11102-019-0103-2.

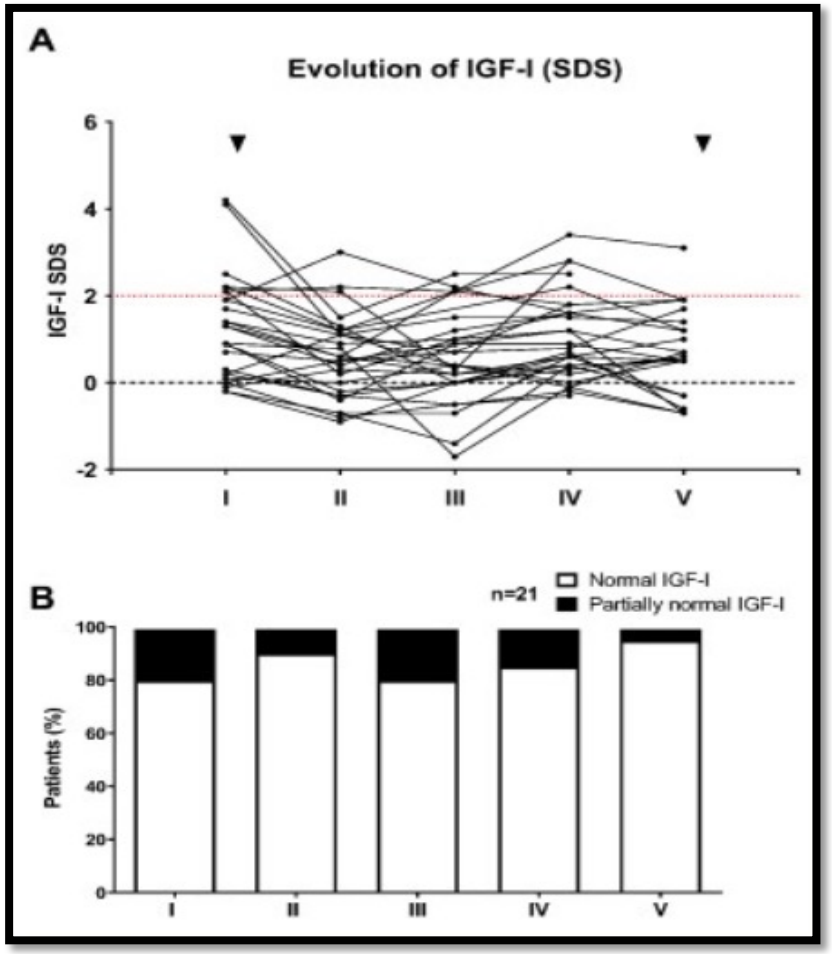
#1449

Assessment of disease control in patients with acromegaly treated with long-acting somatostatin receptor ligands varies according to the time when IGF-I levels are measured during the month following the injection

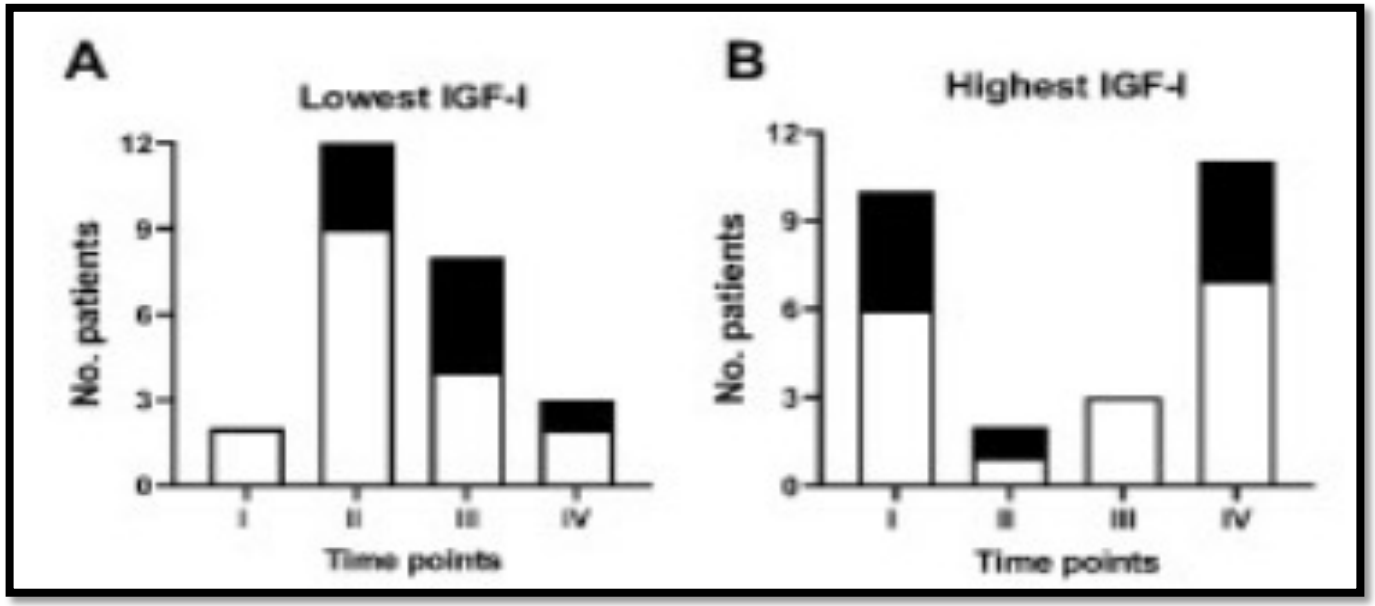
eECE 2020
22nd European Congress of Endocrinology

C **Albrici**[1], A-L **Lecoq**[1], M **Vialon**[2], S **Grunenwald**[2], A **Cocco**[3], S **Hamdi**[2], V **Cimino**[1], L **Maione**[1], P **Caron**[2], P **Chanson**[1]

[1]Assistance Publique-Hôpitaux de Paris, Service d'Endocrinologie et des Maladies de la Reproduction et Centre des Maladies Rares de l'Hypophyse, Hôpital Bicêtre, et Université Paris-Saclay, Le Kremlin-Bicêtre, France; [2]CHU de Toulouse, Département d'Endocrinologie, Hôpital Larrey, Toulouse, France; [3]Politecnico di Milano, Department of Mathematics, Milan, Italy



- Reproducibility between IGF-1 levels measured just before the injection (first sampling) and four weeks later, just before the next injection, was good (*P* = 0.29)
- **A single random IGF-1 does not properly reflect monthly hormone profile in 41.2% of patients.**



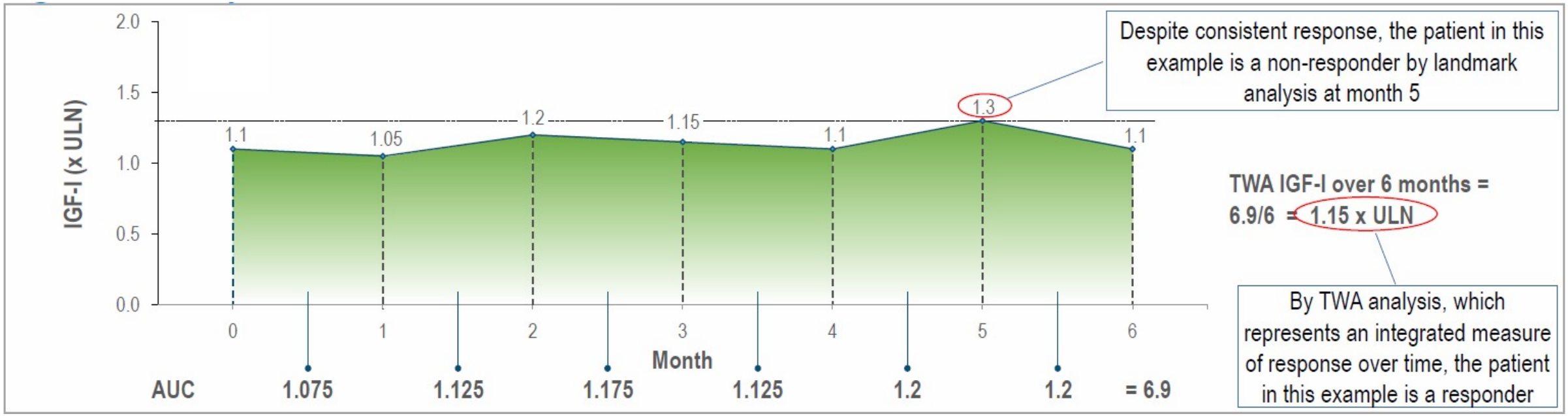
Albrici C, et al. *Endocrine Abstracts*. 2020; 70: AEP665. https://doi.org/10.1530/endoabs.70.AEP665

What is benefit of Time-weighted Average (TWA)

The TWA response, over the treatment period, represents an integrated measure of efficacy across time

TWA Analysis Rationale:

- Helps to minimize the number of missing patients from a primary effectiveness analysis
- Beneficial in accounting for natural variation among the measure of interest that may be observed over the time period of monitoring



Given this approach for calculating the TWA response for an endpoint, no missing value was imputed. However, if a patient discontinued during the RCT phase for lack of efficacy, he/she was considered to be NOT biochemically controlled, regardless of their TWA. Additionally, a sensitivity analysis was conducted to examine the impact of missing data by imputing missing IGF-1 values using the Markov Chain Monte Carlo (MCMC) method for multiple imputation.

Fleseriu et al, AACE 2016 poster

CHIASMA OPTIMAL: Inclusion/Exclusion Criteria

Key Inclusion Criteria

- Adults aged ≥18 years at first screening
- Evidence of active disease (IGF-I ≥1.3 × ULN following most recent pituitary surgery)
- Received injectable SRL therapy for ≥ 6 months
- On stable dose of injectable SRL for ≥3 months
- Average IGF-I ≤1.0 x ULN of 2 screening assessments in response to a stable SRL injection dose

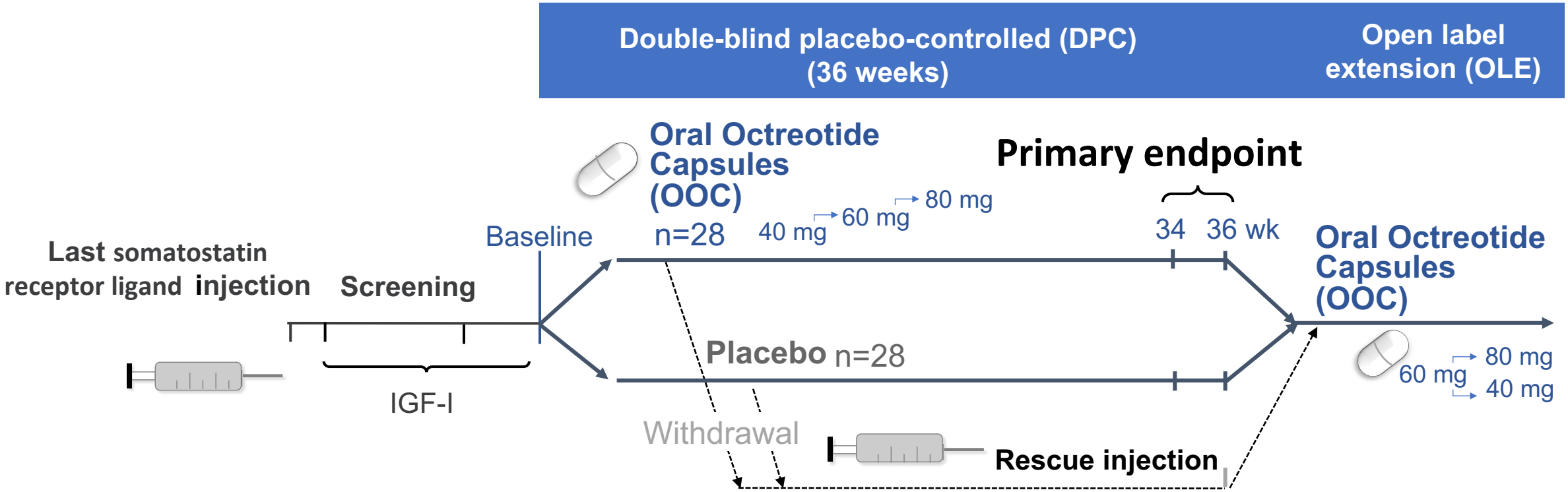
Key Exclusion Criteria

- Receiving off-label doses of injectable SRLs
- Undergone radiotherapy any time in the past or pituitary surgery within 6 months prior to screening
- Receiving pegvisomant within 24 weeks, dopamine agonists within 12 weeks, or pasireotide within 24 weeks before screening

IGF-I, insulin-like growth factor I; SRL, somatostatin receptor ligand; ULN, upper limit normal.

Samson S et al, JCEM 2021

CHIASMA OPTIMAL: Study Design



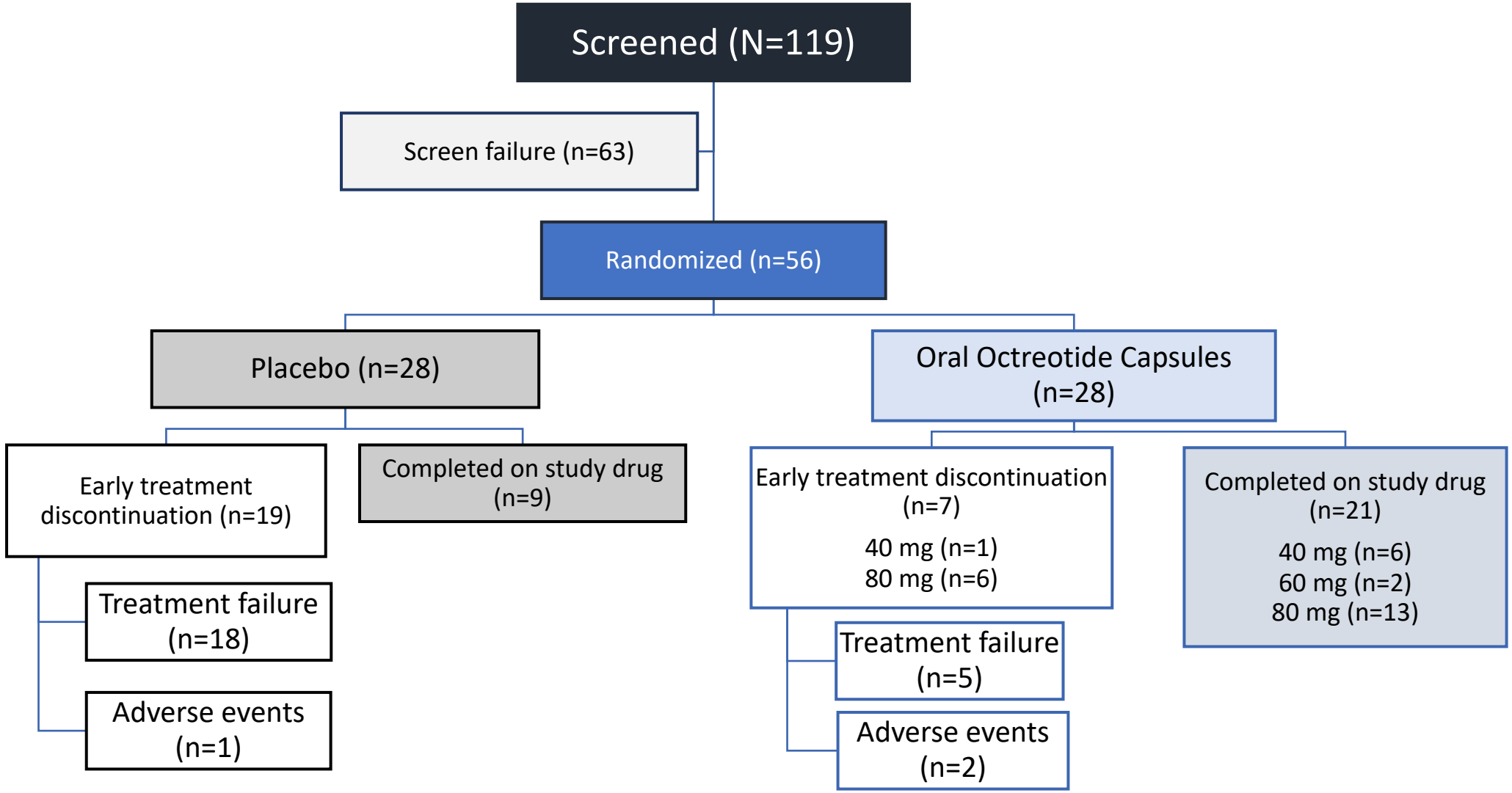
Predefined withdrawal criteria (both arms)

- IGF-I ≥1.3 x ULN for 2 consecutive visits on the highest dose and exacerbation of clinical signs/symptoms
- Early terminated patients followed ≤36 weeks on injections, per protocol

DPC, double-blind placebo-controlled; IGF-I, insulin-like growth factor I; OLE, open-label extension; OOC, oral octreotide capsules; ULN, upper limit of normal.

Samson S et al, JCEM 2021

CHIASMA OPTIMAL: Patient Disposition



Samson S et al, JCEM 2021

CHIASMA OPTIMAL: Baseline Characteristics

	Oral Octreotide Capsules (n=28)	Placebo (n=28)
Sex, Female, n (%)	16 (57.1)	14 (50.0)
Age, y, mean (SD)	55.3 (11.97)	54.2 (10.96)
IGF-I, x ULN, mean (SD)	0.80 (0.16)	0.84 (0.21)
Symptom burden, n (%)		
≥1	23 (82.1)	24 (85.7)
≥2	18 (64.3)	19 (67.9)
≥3	10 (35.7)	14 (50.0)
Weight, kg, mean (SD)	83.4 (17.22)	91.6 (20.48)
BMI, kg/m², mean (SD)	29.1 (6.26)	31.0 (5.58)
Diabetes mellitus, n (%)	2 (7.1)	4 (14.3)

	Oral Octreotide Capsules (n=28)	Placebo (n=28)
Duration of acromegaly, n (%)		
<10 y	15 (53.6)	20 (71.4)
10–20 y	8 (28.6)	5 (17.9)
>20 y	5 (17.9)	3 (10.7)
Prior acromegaly surgery, n (%)	25 (89.3)	24 (85.7)
Prior injectable treatment for acromegaly, n (%)		
Octreotide	19 (67.8)	17 (60.7)
Lanreotide	9 (32.1)	11 (39.3)
Prior injectable dose, n (%)		
Low	6 (21.4)	5 (17.9)
Middle or high	22 (78.6)	23 (82.1)

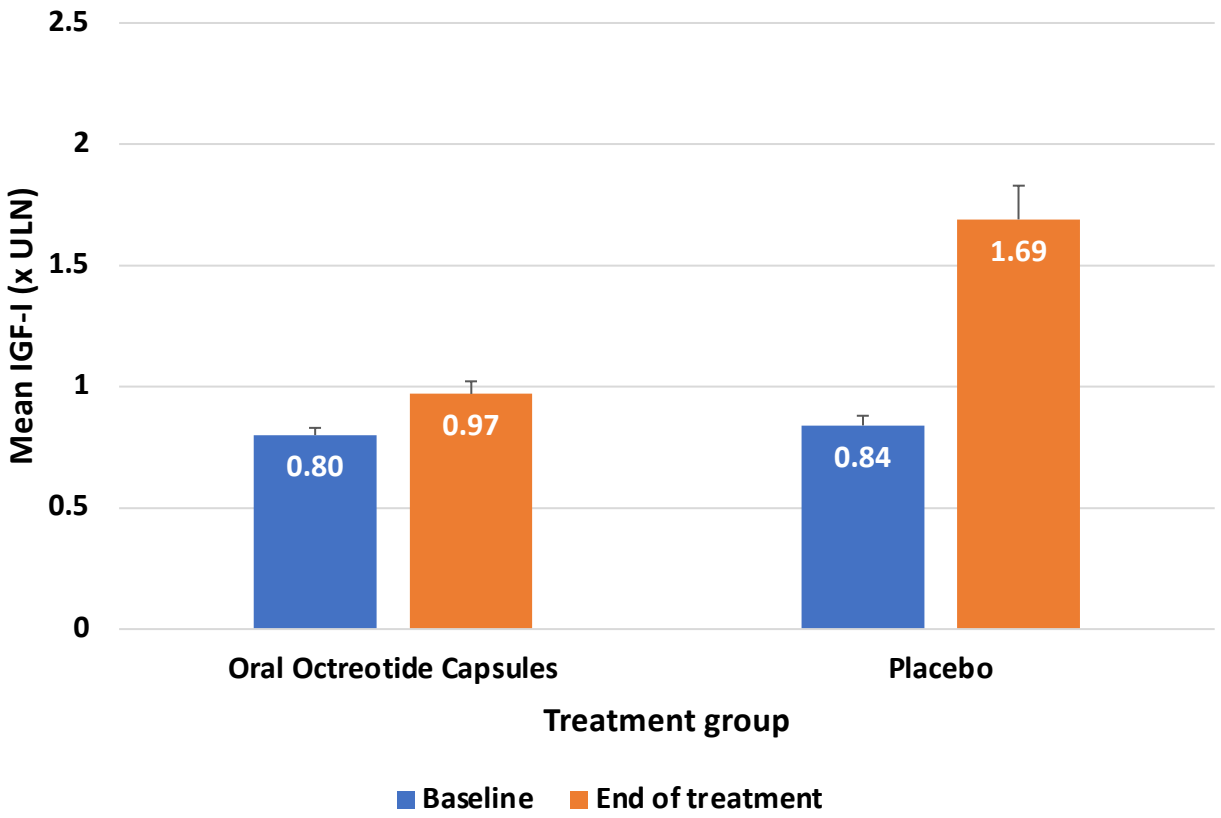
Baseline characteristics relating to demographics and disease and treatment history were well balanced between groups receiving Oral Octreotide Capsules or placebo

Samson S et al, JCEM 2021

BMI, body mass index; IGF-I, insulin-like growth factor I; ULN, upper limit of normal.

Mean IGF-I at Baseline and End of Double-blind, Placebo Controlled Period

Mean IGF-I at Baseline and End of Treatment[a,b]



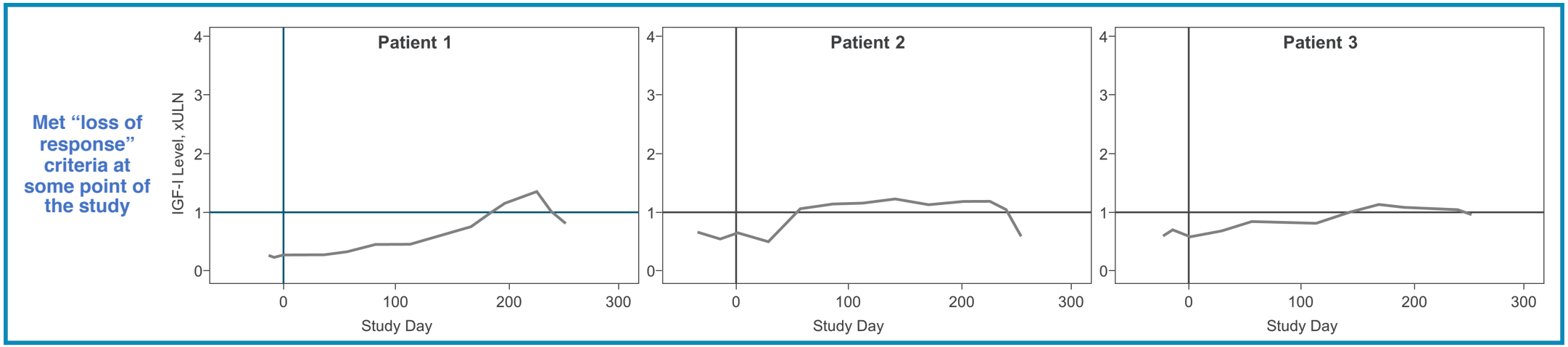
- **Mean IGF-I maintained within normal range in patients receiving Oral Octreotide Capsules**

[a]In patients who reverted to prior injectable SRL, end of treatment measurement was the last measurement prior to reversion to prior therapy; [b]Average of 2 assessments within 2 weeks prior to randomization.
IGF-I, insulin-like growth factor I; SRL, somatostatin receptor ligand; ULN, upper limit of normal.

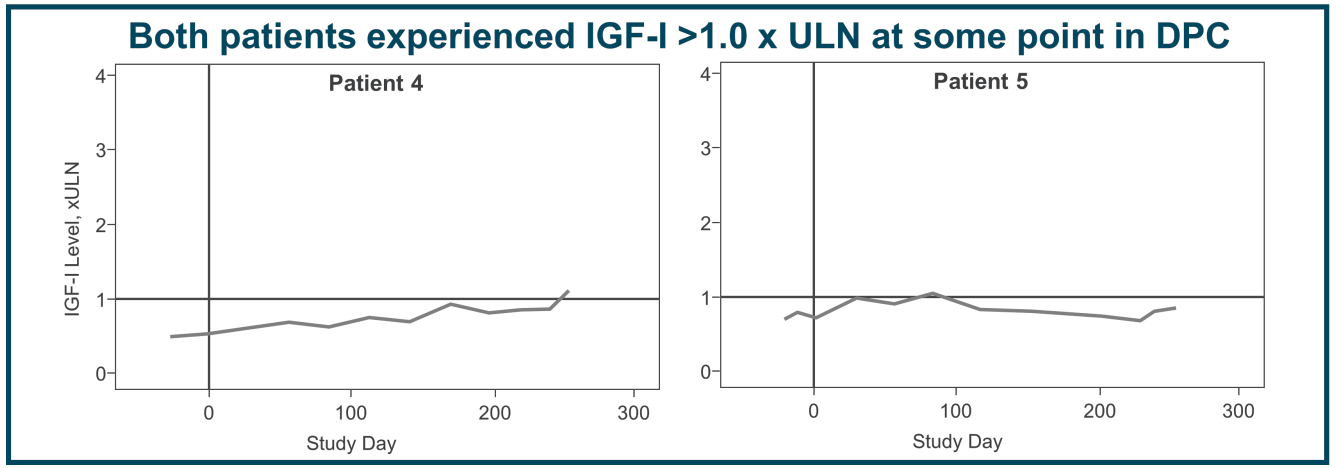
Samson S et al, ECE oral presentation 2020, Samson S et al, JCEM 2021

Majority Of Placebo Group "Responders" Lost Biochemical Control During DPC Phase

3/ 5 patients responding at end of DPC period met "loss of response" criteria at some point of the study



0 of 5 patients were considered disease free



Horizontal line denotes the threshold for "loss of response" criteria (1.0 x ULN)

Vertical line denotes the start of DPC

Clinicians for all 5 patients assessed that each had lost biochemical response or had active acromegaly symptoms

Samson S et al, ECE oral presentation 2020,

Samson S et al, JCEM 2021

DPC, double-blind placebo-controlled; IGF-I, insulin-like growth factor I; ULN, upper limit of normal.

CHIASMA OPTIMAL: Primary and All Secondary Endpoints Met

	Oral Octreotide Capsules (n=28)	Placebo (N=28)	P Value
Primary Endpoint			
Proportion maintaining IGF-I response	58%	19%[a]	0.008
Secondary Endpoints			
Proportion maintaining GH response	78%	30%	0.001
Median time to IGF-I >1.0 x ULN	Not reached in 36 week DPC	16 weeks	<0.001
Median time to IGF-I >1.3 x ULN	Not reached in 36 week DPC	16 weeks	<0.001
Reverted to prior injectable	25%	68%	0.003

[a]All 19% of the placebo responders (n=5) continued in the OLE based on PI discretion, as they either had lost response at some point in the study, or had continuing acromegaly symptoms.
DPC, double-blind placebo-controlled; IGF-I, insulin-like growth factor I; GH, growth hormone; OLE, open-label extension; PI, principal investigator; ULN, upper limit of normal.

Samson S et al, JCEM 2021

CHIASMA OPTIMAL: Safety Results

Most TEAEs were mild or moderate in intensity

AESIs were more common in the placebo group

Subjects With, n (%)	Oral Octreotide Capsules (n=28)	Placebo (n=28)
≥1 Treatment Emergent Adverse Event (TEAE)	28 (100)	27 (96.4)
≥1 Treatment-related TEAE	18 (64.3)	15 (53.6)
≥1 Serious Adverse Event (SAE)	2 (7.1)	1 (3.6)
≥1 Treatment-related SAEs	0	0
≥1 Maximum severity severe TEAE	3 (10.7)	7 (25.0)
≥1 TEAE leading to study drug discontinuation	2 (7.1)	1 (3.6)
≥1 Adverse event of special interest (AESI, acromegaly symptoms)[a]	15 (53.6)	26 (92.9)

[a]TEAEs of special interest includes: headache, fatigue, perspiration, soft tissue swelling, arthralgia, dysglycemia, hypertension, or other signs in view of investigator as related to acromegaly.
AESI, adverse event of special interest; DPC, double-blind placebo-controlled; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Samson S et al, JCEM 2021

CHIASMA OPTIMAL

Oral Octreotide Capsules (OOC) may be a potential option in the management of patients with acromegaly currently controlled by injectable SRLs

CHIASMA OPTIMAL met all primary and secondary endpoints

- 75% of patients on OOC completed 36 weeks without need for reversion to prior injectable therapy
- Mean IGF-I was maintained within the normal range for patients receiving OOC
- Median time to loss of response in the placebo group was 16 weeks; this was not met in the OOC group by 36 weeks
- 58% of patients receiving OOC maintained response at the end of the DPC period
- 90% of the OOC group chose to continue in extension

The safety profile of OOC was consistent with the known safety profile of octreotide

- No new/unexpected safety signals were observed
- Most AEs were mild to moderate in intensity; GI AEs were transient in nature
- AESIs were more common in the placebo group

AE, adverse event; AESI, adverse event of special interest; DPC, double-blind placebo-controlled; IGF-I, insulin-like growth factor I; GI, gastrointestinal; OOC, oral octreotide capsules.

Samson S et al, JCEM 2021, Labadzhyan A et al, Pituitary 2021

MYCAPSSA®

SHEILA FRAME , PRESIDENT, AMERICAS

DR. MARK SUMERAY, CMO

RORY NEALON, CFO/COO

MYCAPSSA® - ACROMEGALY - MARKET OVERVIEW

Acromegaly is a rare disease most often caused by a ***benign pituitary tumor*** and characterized by an excess of growth hormone and insulin-like growth factor-1 hormone. Treatment options include surgery, medication and radiation or a combination of these.

If untreated, acromegaly may cause:

Altered facial appearance | Enlargement of the hands and feet | Type 2 diabetes | Intense headaches | Joint pain | Respiratory disorders | Cardiac disease | Cerebrovascular disease | Enlarged organs

Octreotide and lanreotide injections are broadly used as **first-line** pharmacological treatments

Injections Present Significant Challenges to Patients**

The global market for SSAs in the treatment of acromegaly is estimated at ~$800 million with US estimated at ~$400 million*

Mycapssa® is the first and only FDA-approved oral somatostatin analog (SSA) for appropriate patients with acromegaly, providing effective and consistent biochemical control while reducing the treatment burden associated with injectable therapies.

*Management estimate based on 2019 available market data.
**Strasburger, et al. Patient reported outcomes of parenteral somatostatin analogue injections in 195 patients with acromegaly. Eur J Endocrinology. 2016 Mar; 174(3):355-62

MYCAPSSA® - STANDARD OF CARE IMPACT

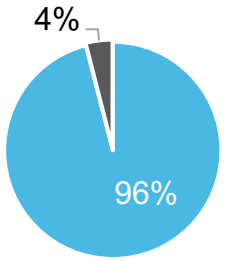
THE FOUNDATION IS IN PLACE

HCPs

Familiarity with Octreotide

HCPs will draw on past experience with octreotide

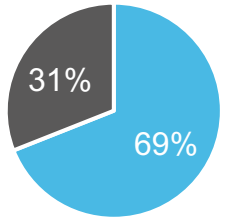
HCP Intent to Prescribe[1]



96% of endocrinologists report likely to grant a patient's request to switch to Mycapssa® (n=50)

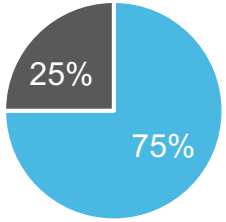
Patients[2]

Positive Patient Feedback



69% of patients considering or open to considering Mycapssa® (n=29)

Informed Patients



75% of patients familiar with Mycapssa® (n=40)

Payers

Over 185M Lives Covered[3]

- Payers see the value in offering Mycapssa®
- Creating access and choice for patients

Compelling Value for Payers

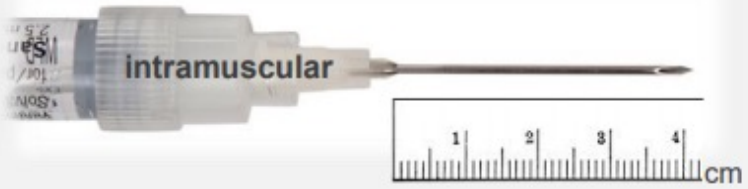
- Oral Option addresses unmet need
- SSAs already reimbursed and in payers' budgets
- Mycapssa® pricing designed to facilitate broad access

[1]Source: KANTAR Survey fielded from February/March 2021, N=50 (US licensed endocrinologists treating acromegaly patients with SSAs)
[2]Source: Survey fielded from 2/23/2021 to 3/8/2021, N=47 (39 patients, 2 caregivers, 6 other)
[3]Covered lives in US of 3/31/2021

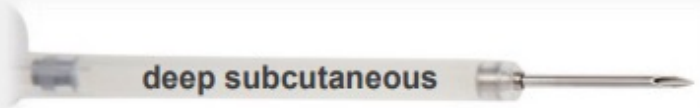
AMRYT PHARMA

INJECTIONS CARRY SIGNIFICANT TREATMENT BURDENS[1]

Novartis' Octreotide LAR: 19 or 20 Gauge



Ipsen's Lanreotide Depot: 18 or 19 Gauge



Reference: Insulin Needle: 30 Gauge

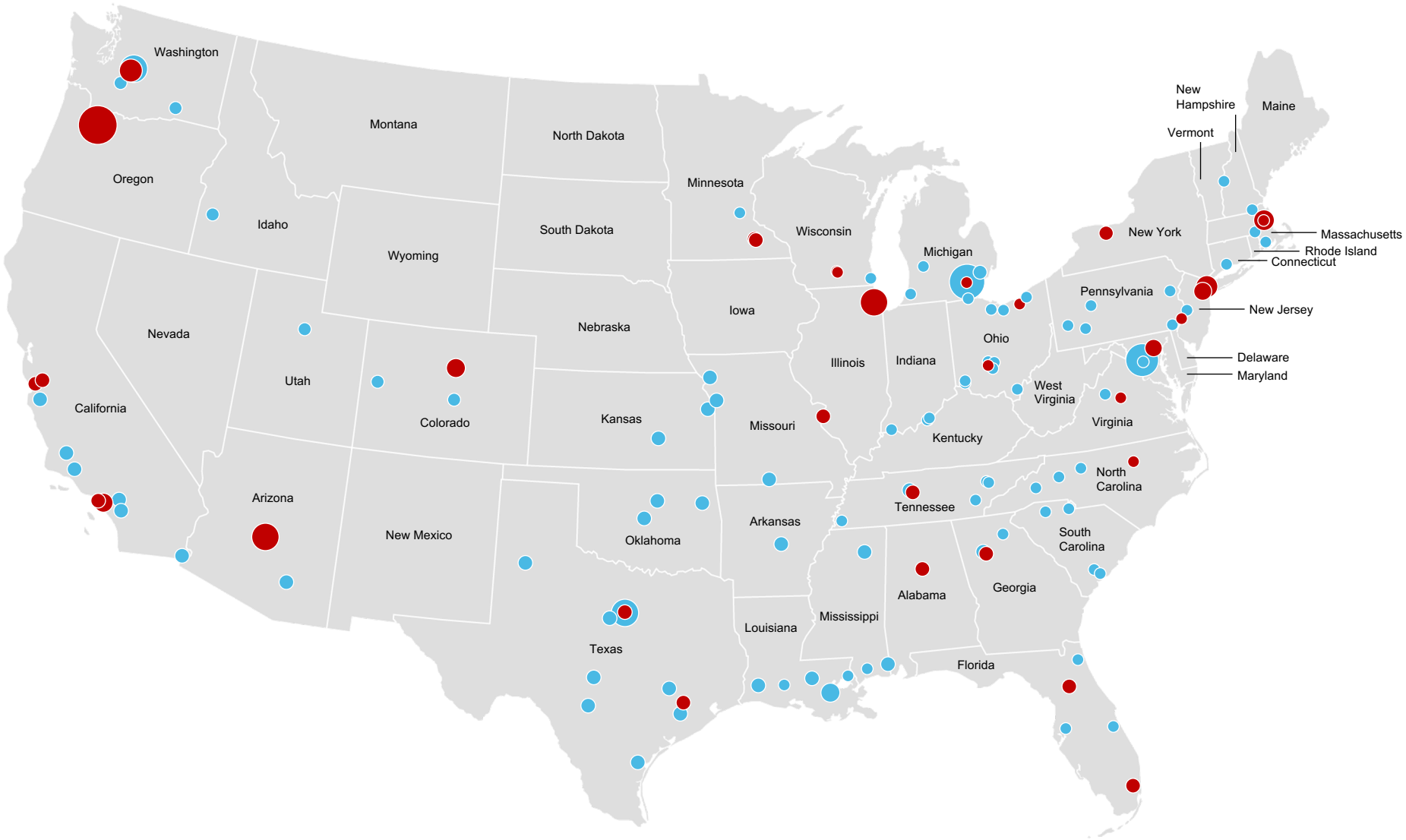
Pain	**70%**	experience pain **during injection**; half of these experienced continuing pain days later
Injection Site Reactions		Hardness **(48%)**, nodules **(38%),** swelling **(28%)**, bruising **(16%)** and inflammation **(7%)**
Suboptimal Symptom Control	**52%**	report symptoms worsen toward the end of the monthly dosing interval
Emotional Impact	**36%**	feel **loss of independence** due to chronic injections
Lost Workdays	**16%**	regularly **miss work** for injections (averages 11 days/year)

[1] Source: Strasburger et al. Patient reported outcomes of parenteral somatostatin analogue injections in 195 patients with acromegaly. Eur J Endocrinol. 2016 Mar;174(3):355-62.

ENDO TARGETS OVERLAP PRESENTS AN OPPORTUNITY TO BROADEN COVERAGE FOR BOTH MYCAPSSA® AND MYALEPT®

Mycapssa® + Myalept® HCP Endo and PTC targets

- Mycapssa PTCs
- Myalept HCPs



AMRYT PHARMA

MYCAPSSA® - FOCUS TO ACCELERATE UPTAKE IN THE US

- Leverage inside sales team to pre-screen open offices and secure stronger focus on community endocrinologist
- Combine and train endocrinology commercial teams (Mycapssa® + Myalept®) to extend reach and breadth by increasing the field sales team
- Integrate the Medical Affairs endocrinology expertise by increasing the field medical team, to engage endocrinologists with emerging data
- Build stronger patient support program and services to better support patient transition from injection to capsule. Work with patients and prescribers to appropriately manage initiation and titration for persistence to improve patient outcomes

Mycapssa® is the first and only somatostatin analogue (SSA) capsule for the management of appropriate patients with acromegaly

MYCAPSSA® - DEVELOPMENT OPPORTUNITY IN NET

- In the U.S. c. 24,000* Neuroendocrine Tumor (NET) patients are treated with SSA injections
- Primarily non-pancreatic GI-NETs cause carcinoid syndrome in patients
- Majority of these patients receive SSA to limit tumor progression and treat carcinoid syndrome
- Injectable formulations of octreotide are the existing standard-of-care in the management of NET
- Mycapssa® is potentially well-positioned to address the unmet need in the SSA therapy arena for NET**
- Patients (as with acromegaly) experience high treatment burden with injectables and HCPs / patients have expressed high interest in additional treatment options

* National Cancer Institute SEER Database; Halperin et al. 2017 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6066284
**Further studies required

MYCAPSSA® - DEVELOPMENT OPPORTUNITY IN NET CONT'D

- Oral SSA may provide more convenient and less painful delivery and can be administered at home
- Mycapssa® has potential for improved efficacy over current SoC with "continuous disease control"
- Regulatory / HCP familiarity and comfort with octreotide
- Mycapssa® has demonstrated therapeutic equivalence with injectable formulations of octreotide in the management of acromegaly
- The main risk to approvability is the extent to which oral administration achieves adequate and consistent within-patient bioavailability to provide adequate control of symptoms at a tolerated dose level

MYCAPSSA® - REGULATORY PATHWAY FOR NET APPROVAL

- FDA Alignment
  - In principle single Phase 3 NET registrational trial focused on carcinoid syndrome symptoms utilizing 505(b)(2) pathway
- Target indication
  - Long-term treatment of severe diarrhea and flushing episodes associated with metastatic carcinoid tumors (same as Sandostatin LAR)
- PIND Written Response Only FDA feedback (Nov and Dec 2020)
  - No additional pre-clinical work needed
  - DDI and PK studies needed in addition to pivotal Phase 3 trial

MYCAPSSA® - REGULATORY PATHWAY FOR NET CONT'D

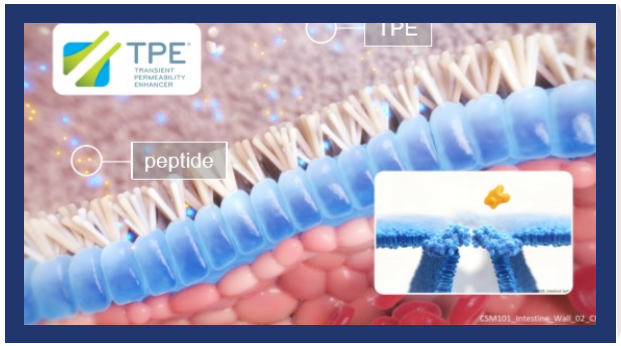
- Type C meeting with FDA June 2021
  - Good progress with discussion on disease, treatment and complications
  - Agreed potential study design for Phase 3
- Plan to complete PK study to establish bioavailability of octreotide at higher doses of Mycapssa® vs injectable and Type C meeting with FDA Q4 2021 to finalize study design for Phase 3
- Plan to initiate study in 2022 and file NDA in 2024

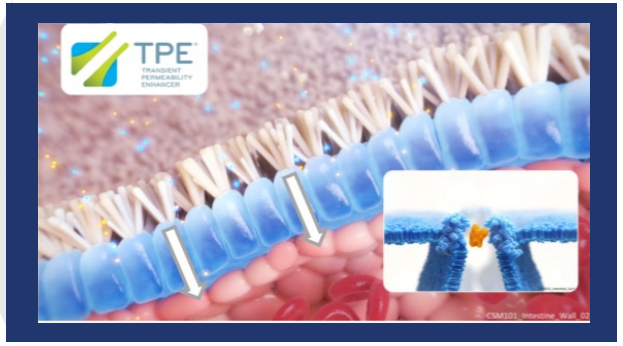
TPE - VALIDATED DELIVERY TECHNOLOGY PLATFORM

With the approval of Mycapssa®, the TPE* represents a validated technology delivery platform for potential new development opportunities

Capsules with TPE technology have an enteric coating to protect against degradation in the stomach.

Once in the small intestine, the capsule is designed to dissolve and release the TPE formulation.





TPE technology induces the reversible expansion of tight junctions between intestinal epithelial cells, a natural process to absorb nutrients.

Capsules containing TPE can allow drug therapies to enter systemic circulation while excluding toxins, bacteria and viruses.

*TPE – Transient Permeability Enhancer

KEY AREAS OF FOCUS FOR SYNERGIES

Overall Objective – Migrate Chiasma retained employees to existing Amryt infrastructure

- **Headcount related savings**
  - Reduction in duplication of roles
    - Day 1 leavers, including C-suite
    - Leverage off existing Amryt infrastructure which has bandwidth to take on an additional commercial asset, transitioning various Chiasma employees out over 1-12 months transition period
  - Migration of certain roles to Ireland, resulting in facilities and staff cost reductions
  - Future headcount recruitment savings

KEY AREAS OF FOCUS FOR SYNERGIES CONT'D

Other Operating Expenditure related savings

- In-sourcing current elements of Chiasma operating expenses, including external regulatory, PV and clinical consulting costs
- Leveraging off existing systems, with significant synergies to be achieved in IT and quality platforms
- Eliminating duplicate vendors/ services, e.g. audit and tax fees, IR/ PR services, company secretarial/ listing fees
- Leveraging Amryt management's experience with new product launches and Amryt's existing presence in endocrinology resulting in more focused and strategic commercial and medical affairs spend

Questions & Answers

AMRYT PHARMA