New Horizon in Medical Management of Acromegaly

Nahid Hashemi Madani

Institute of Endocrinology and Metabolism
Iran University of Medical Science

Agenda

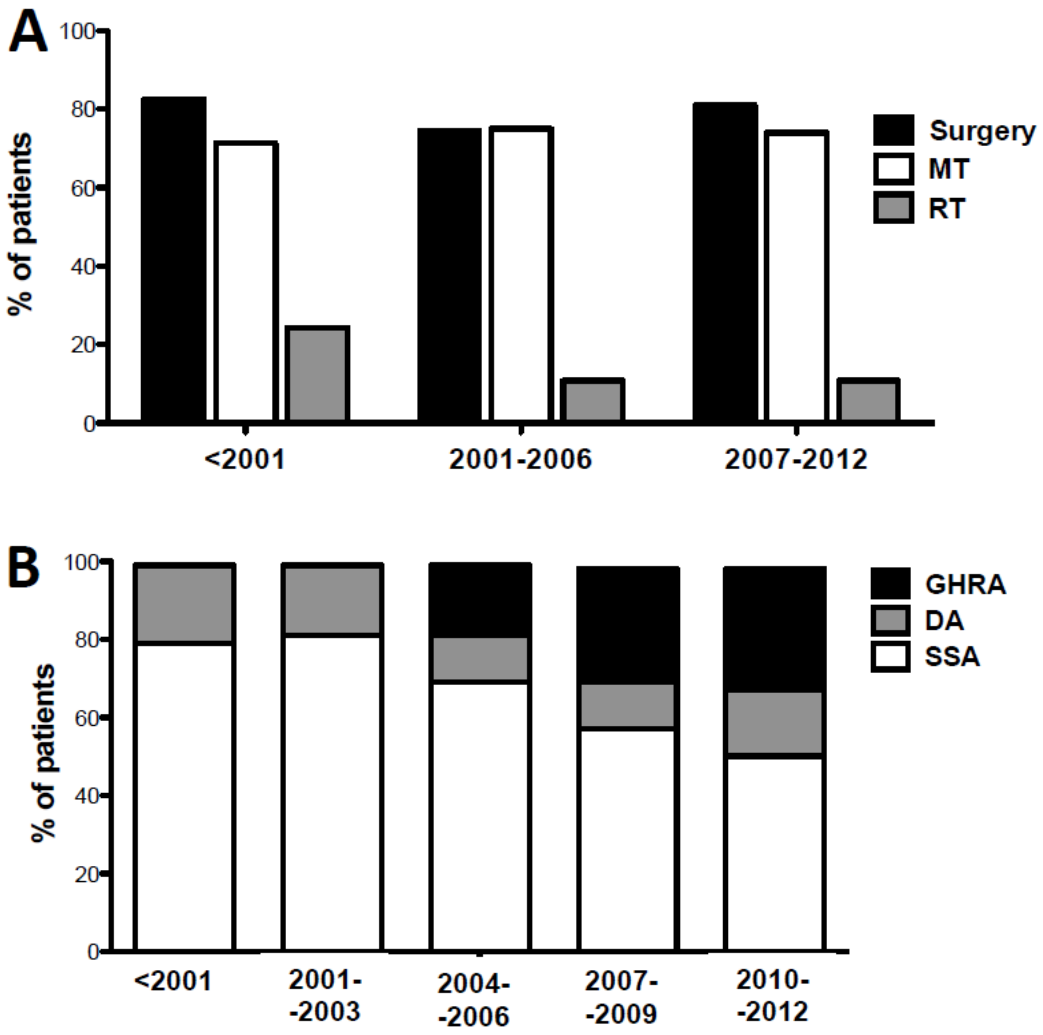
- Evolution of treatment strategy
- Proposed place of medical therapy
- Available medications
- Novel medications

Treatment modalities

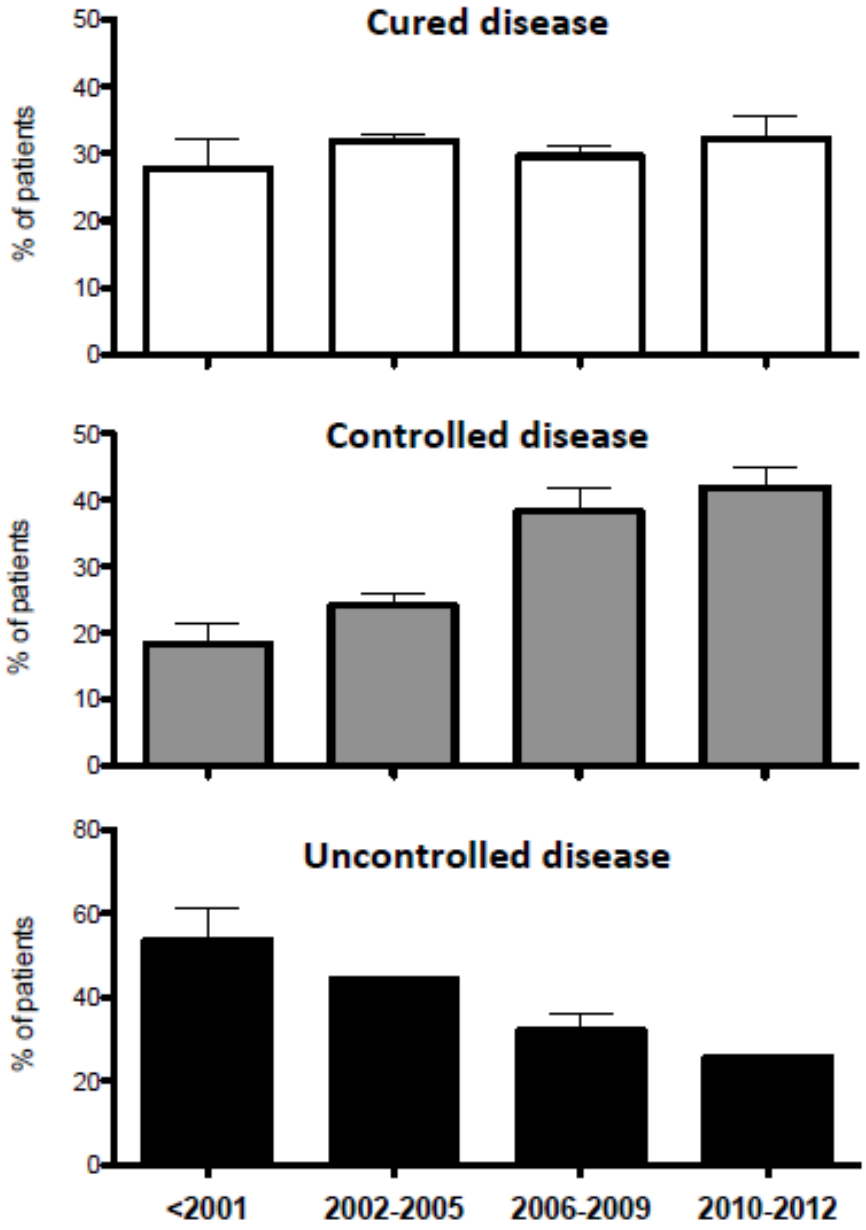
- Surgery
- Medical therapy
- Radiotherapy

Evolution of treatment strategy

French Registry
33 centers
999 patients



European Journal of Endocrinology **2017 176 645–655**



European Journal of Endocrinology **2017 176 645–655**

Proposed Place of Medical Therapy

- **Persistent disease after surgery**

- **Preoperative :**

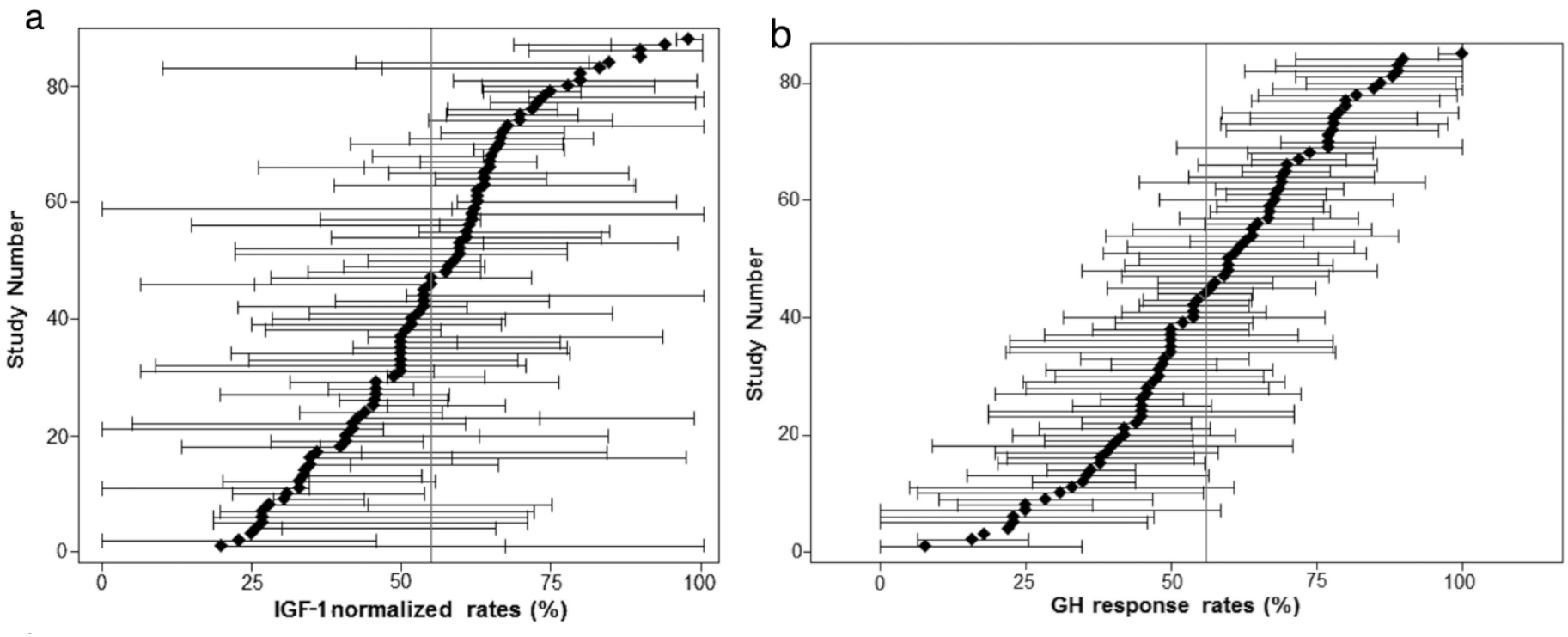
  uncontrolled metabolic status

  difficult intubation due to severe pharyngeal thickness

  high output heart failure

Available Medications

IGF-1 and GH response rates to octreotide/lanreotide for the 90 analyzed cohorts

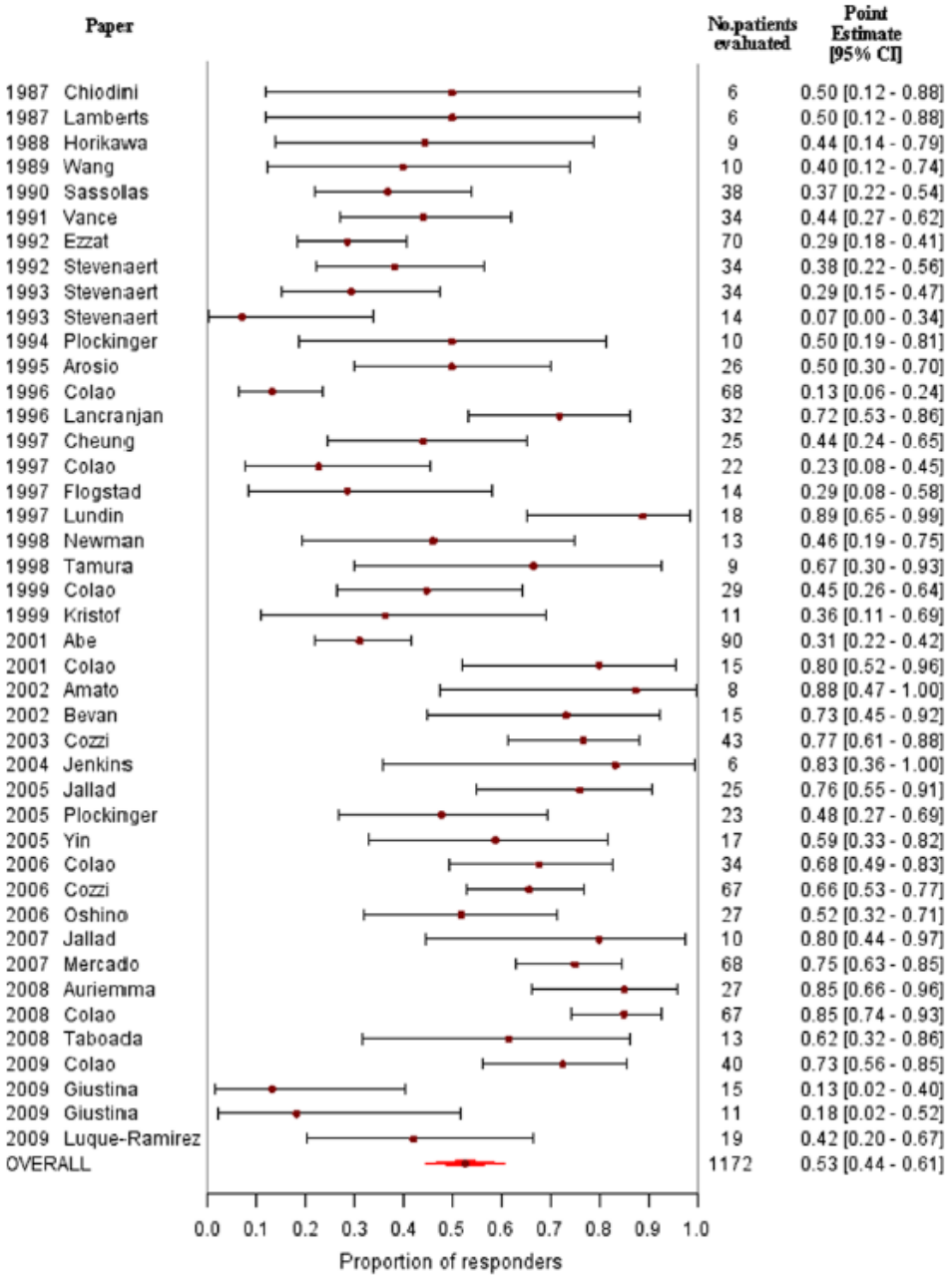


J Clin Endocrinol Metab, May 2014, 99(5):1825–1833

Effect of Octreotide on tumor mass, meta-analysis of 41 studies

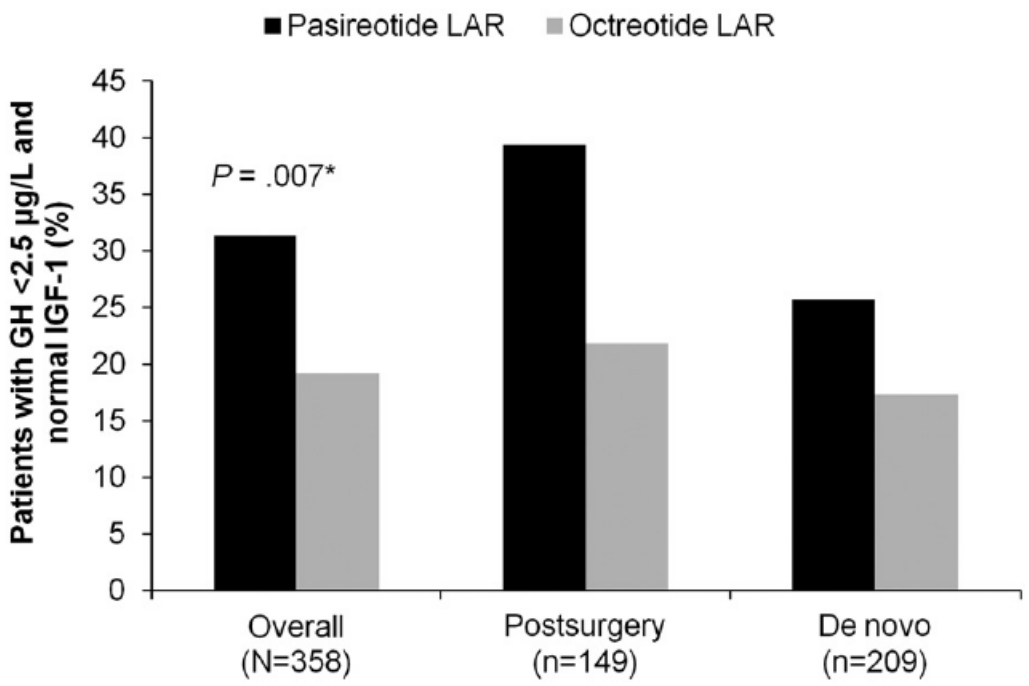
Determinants of response:

- Safe GH level
- Nl IGF-1
- Oct LAR
- Duration>1yrs



***PLoS One*. 2012;7:e36411**

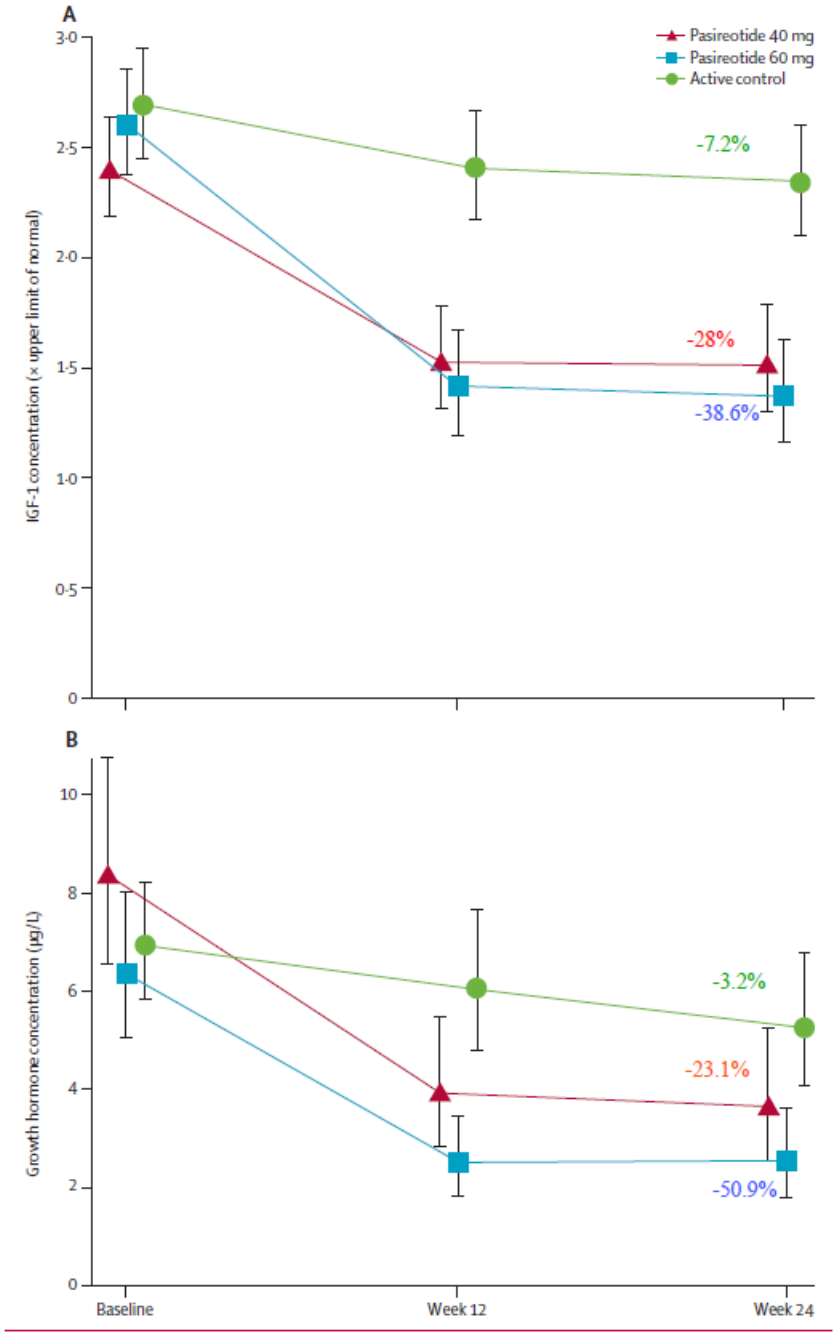
Pasirotide vs Octreotide in acromegaly



12 months

J Clin Endocrinol Metab, March 2014, 99(3):791–799

N:354
On OCT/LAN>6 mo
Inadequate response:
IFG-1>1.3ULN
GH>2.5ng/ml

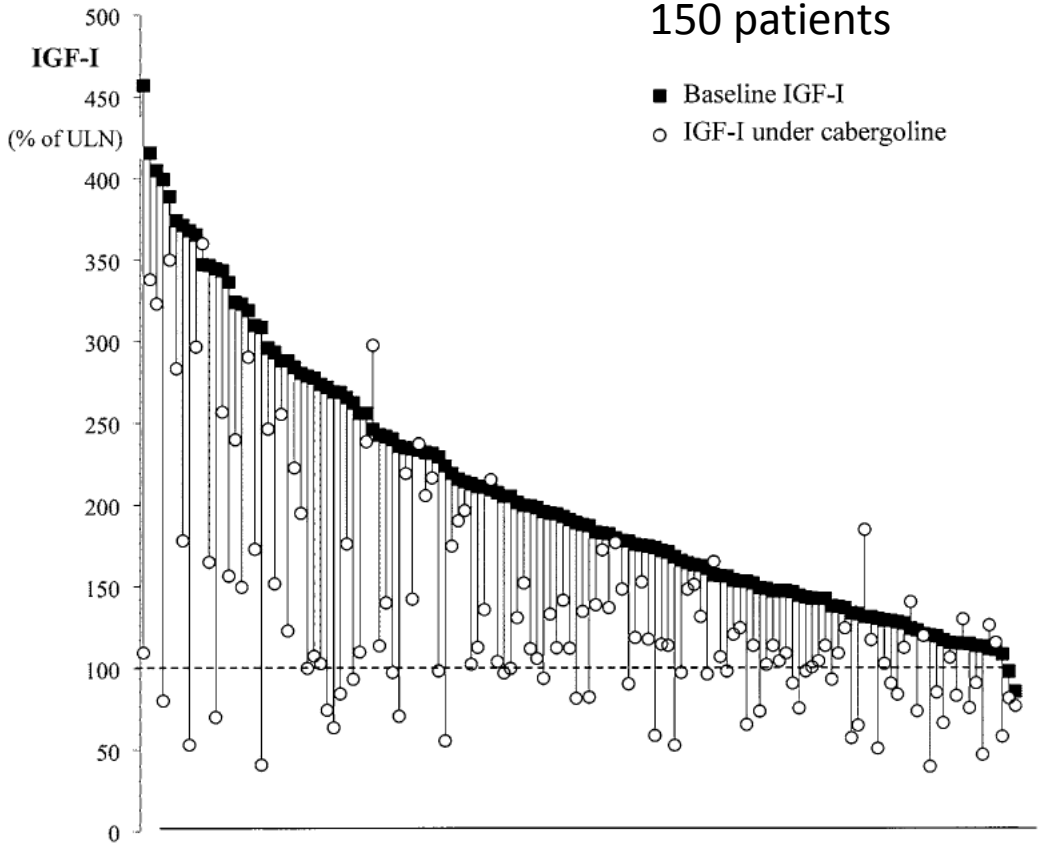


Lancet Diabetes Endocrinol. **2, 875–884 (2014)**

IGF-1 response rates to Caberguline

Nl IGF-1 in 34%

9 studies
150 patients



Determinants of Nl IGF-1:

- **Baseline IGF-1 <1.8** ULN in the normalized group vs >2.2 in the non-normalized group ;p=0.01)

- **Previous RT**

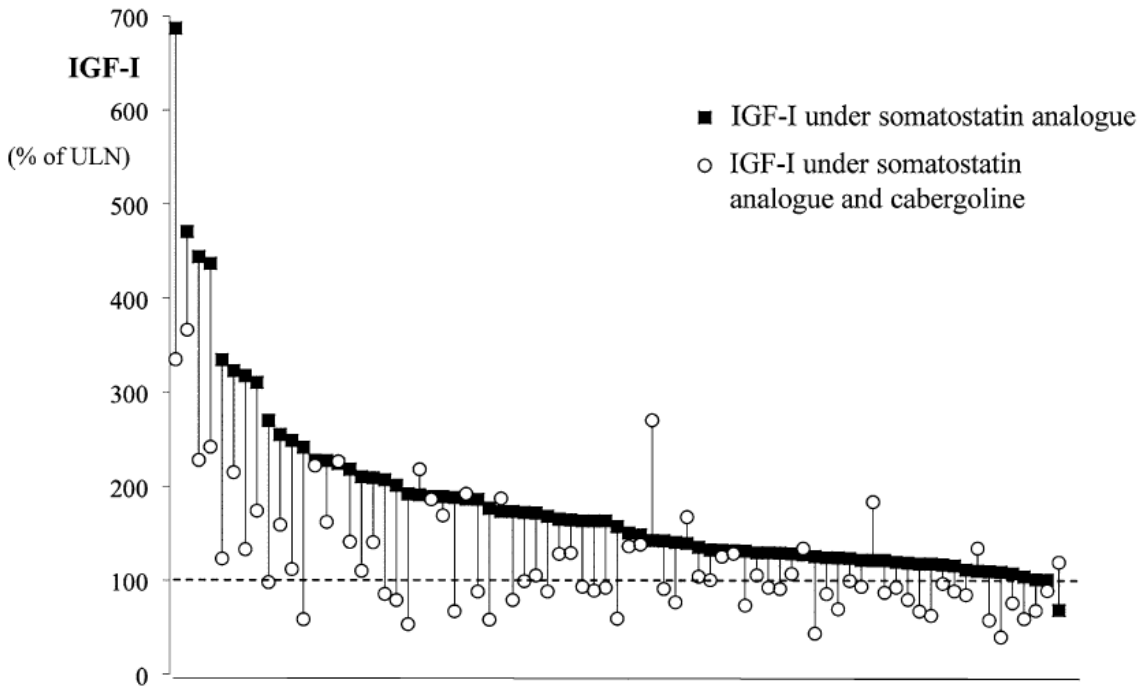
J Clin Endocrinol Metab, 2011,96(5):1327–1335

5 studies
77 patients

Nl IGF-1 in 52%

<u>Determinant of Nl IGF-1:</u>

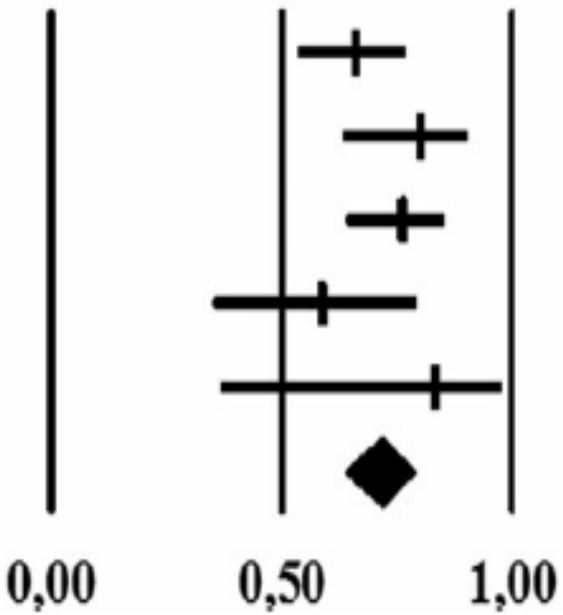
Baseline IGF-1: 1.4 uln in normalized group vs 2.2 uln in non-normalized group; p<0.001



J Clin Endocrinol Metab, 2011,96(5):1327–1335

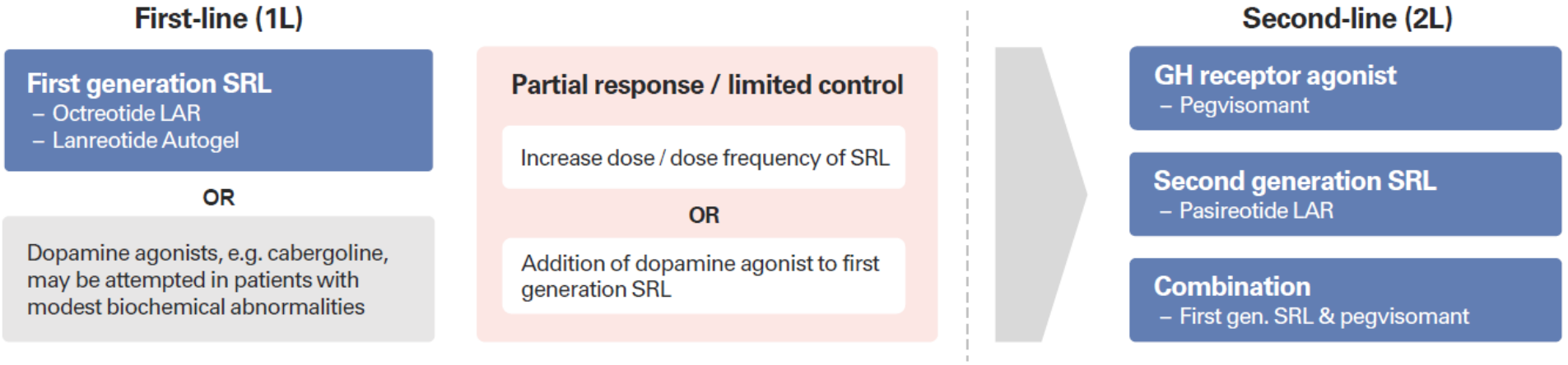
IGF-1 control under PEG monotherapy

Study name	Event rate	Lower limit	Upper limit
Berg, 2010	0,661	0,536	0,768
Bianchi, 2013	0,800	0,636	0,902
Bernabeu, 2016	0,762	0,642	0,851
Basalvibaso, 2016	0,588	0,352	0,790
Kasuki, 2016	0,833	0,369	0,977
	0,717	0,640	0,784



Endocrine (2019) 63:18–26

Proposed algorithm for the treatment of acromegaly



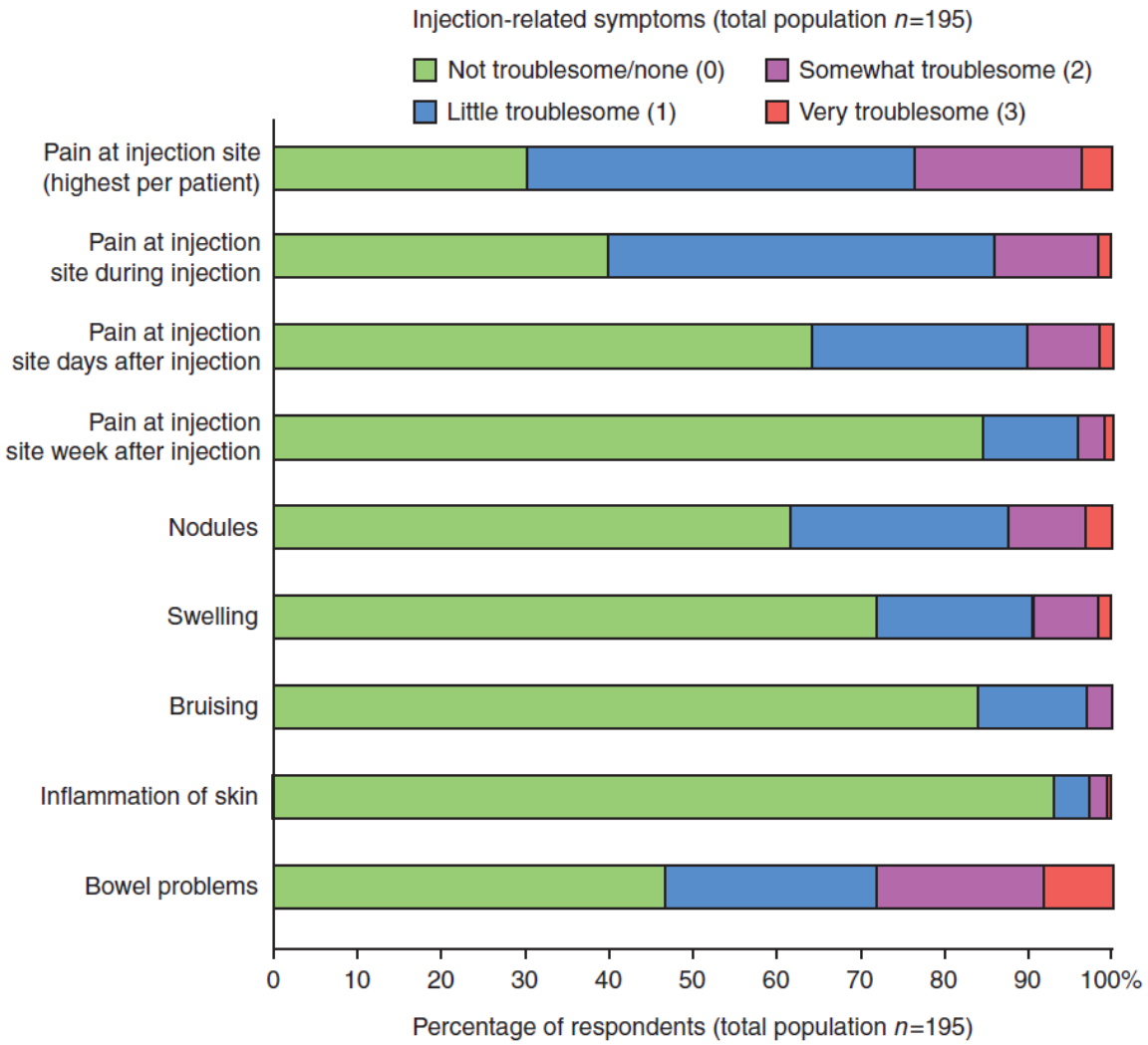
*Nat RevEndocrinol.*2018;14(9):552-561, *European Journal of Endocrinology* (2019) 181

Challenges with available somatostatin analogues

	Pasireotide LAR, n = 178[a]		Octreotide LAR, n = 180[a]	
	All Grades, n (%)	Grade 3/4, n (%)	All Grades, n (%)	Grade 3/4, n (%)
Diarrhea	70 (39.3)	1 (0.6)	81 (45.0)	4 (2.2)
Hyperglycemia	51 (28.7)	6 (3.4)	15 (8.3)	1 (0.6)
Cholelithiasis	46 (25.8)	1 (0.6)	64 (35.6)	2 (1.1)
Diabetes mellitus	34 (19.1)	9 (5.1)	7 (3.9)	0
Headache	33 (18.5)	2 (1.1)	46 (25.6)	5 (2.8)
Abdominal pain	32 (18.0)	1 (0.6)	40 (22.2)	0
Alopecia	32 (18.0)	0	35 (19.4)	0
Nasopharyngitis	28 (15.7)	0	28 (15.6)	0
Nausea	24 (13.5)	1 (0.6)	39 (21.7)	0
Increased blood creatine phosphokinase	23 (12.9)	3 (1.7)	21 (11.7)	4 (2.2)
Abdominal distension	21 (11.8)	1 (0.6)	21 (11.7)	1 (0.6)
Arthralgia	17 (9.6)	1 (0.6)	22 (12.2)	1 (0.6)
Fatigue	17 (9.6)	1 (0.6)	18 (10.0)	0
Dizziness	17 (9.6)	0	19 (10.6)	0
Back pain	14 (7.9)	0	20 (11.1)	2 (1.1)

J Clin Endocrinol Metab, March 2014, 99(3):791–799

Challenges with available somatostatin analogues



European Journal of Endocrinology (2016) 174, 355–362

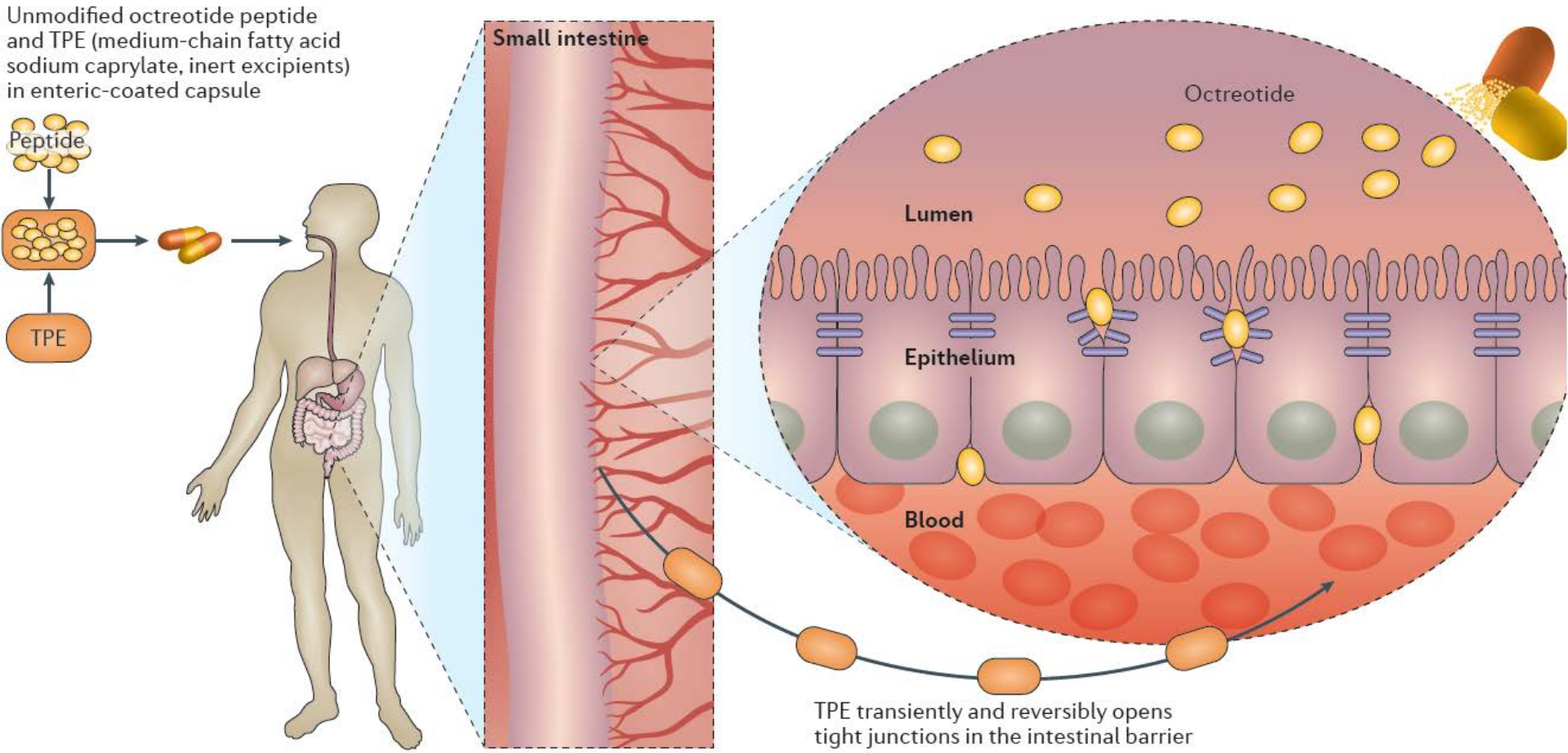
Challenges with available somatostatin analogues

- Injections need to be **intramuscularly** with a **rather large needle** (19 G)
- Complex **reconstitution before injection** and prone to **needle clogging**
- Absence of self-administration
- Requires **refrigerator**
- Drug release is **not linear**

Novel medications

Oral Octreotide

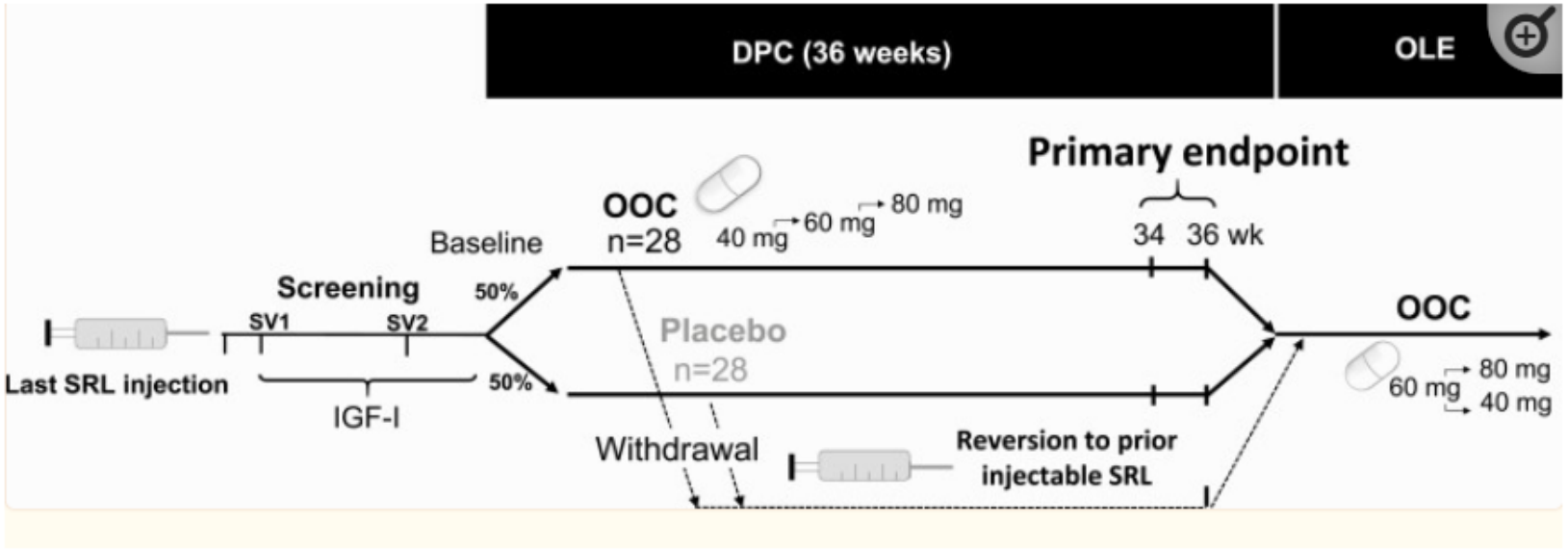
20 mg OOC ~ 100 µg iOCT



Transient permeability enhancer

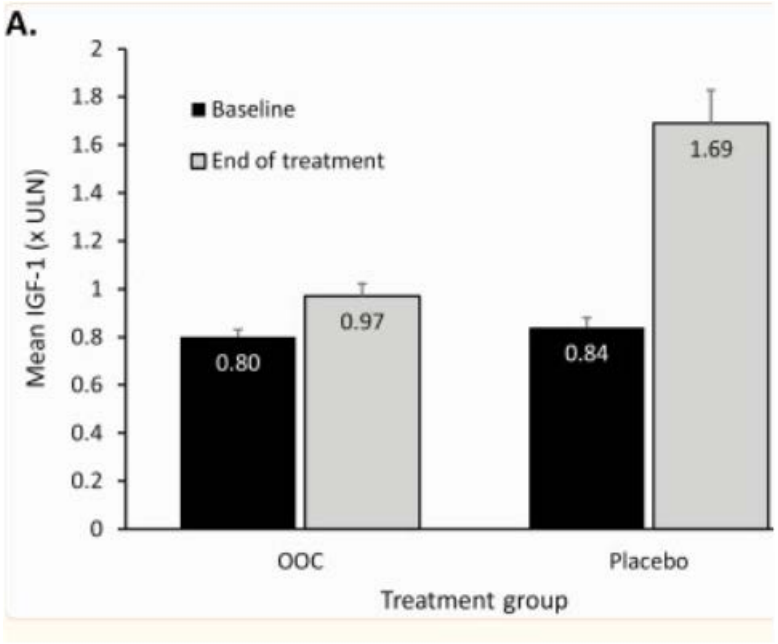
NATURE REVIEWS, ENDOCRINOLOGY,2015

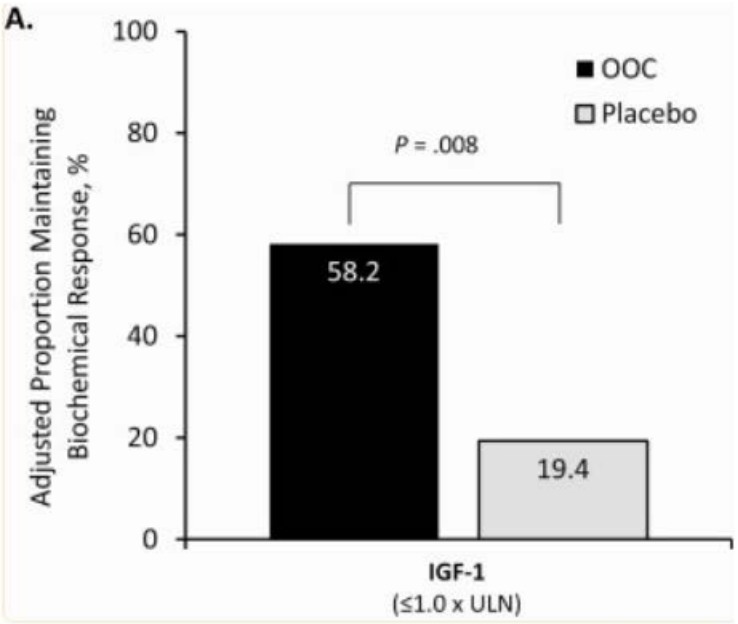
The Phase 3 CHIASMA OPTIMAL trial



N:56
On iOCT/LAN>3mo
NL IGF-1

JCEM,2020 Oct; 105(10)





FDA approval for **maintenance therapy** in patients controlled by OCT/LAN

JCEM,2020 Oct; 105(10)

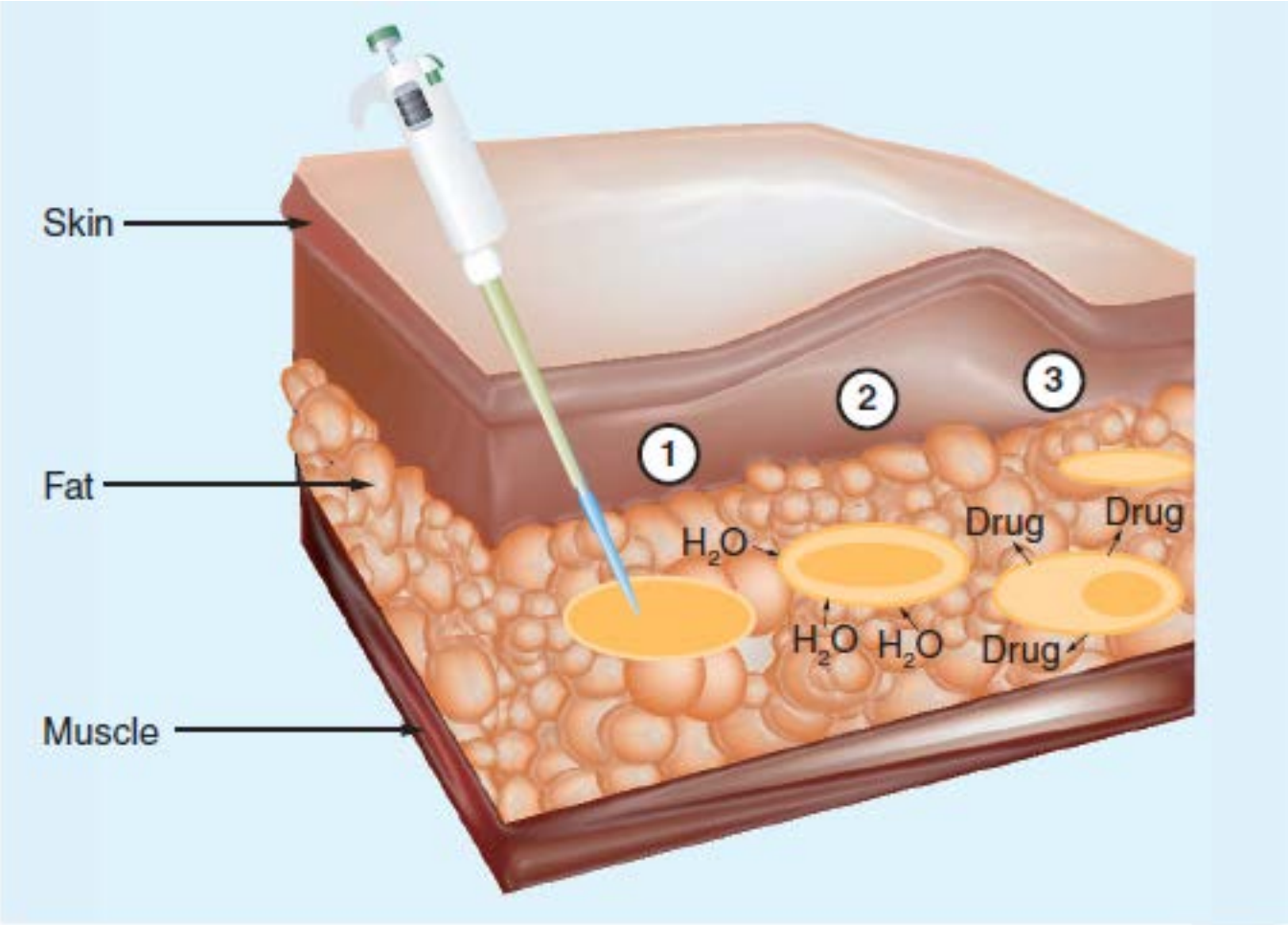
Maintenance of response to oral octreotide compared with injectable SRL

	Oral octreotide (n=55)	iSRL (n=37)	Adjusted difference in proportions
Primary endpoint			
Biochemical responders in randomised treatment phase	50 (91%, 44–53)	37 (100%, 34–37)	−9·1% (−19·9 to 0·5)

- 92 patients on iSRLs for > 6 months
- Biochemical response: IGF-1<1.3ULN **and** GH<2.5 ng/ml

Lancet Diabetes Endocrinol **2022; 10: 102–11**

CAM2029 (sc. Depot Octreotide)



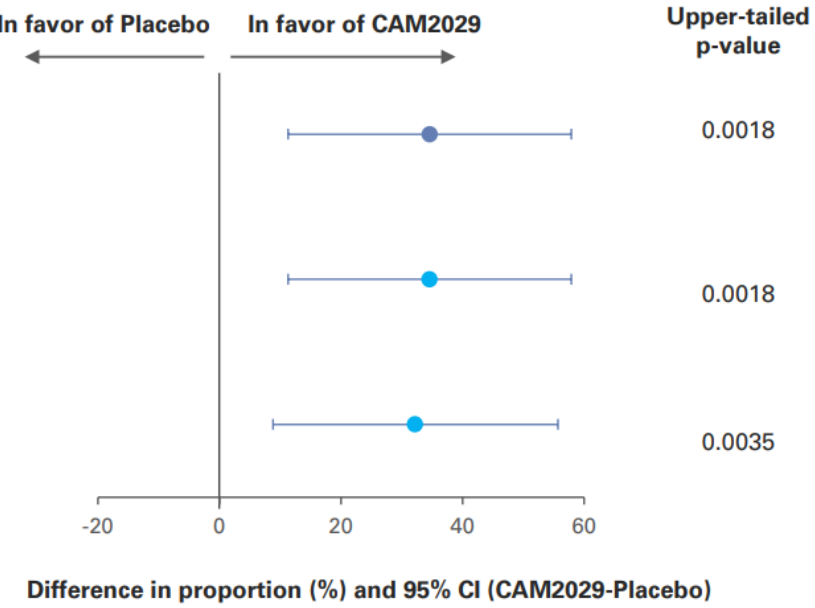
More bioavailability
More rapid onset
Similar duration of action

Ther. Deliv. **(2017) 8(10)**

ACROINNOVA

Phase 3, Randomised, double-blind, placebo-controlled, trial of octreotide sc. Depot
N:72
On iSRLs > 3mo : NL IGF-1 **AND** GH<2.5 ng/ml

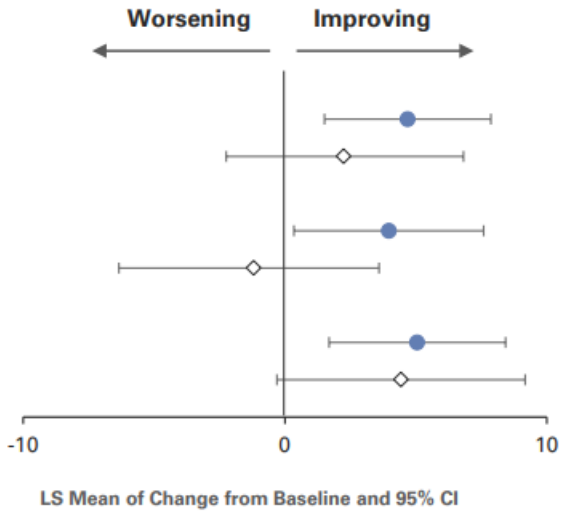
	CAM2029 % responders	Placebo % responders	CAM2029-Placebo % (95% CI)	Upper-tailed p-value
Primary efficacy endpoint - Proportion of patients with mean IGF-1≤ULN at Week 22 and Week 24	72.2	37.5	34.6 (11.3, 57.9)	0.0018
Key secondary efficacy endpoint - Proportion of patients with mean IGF-1≤ULN at Week 22 and 24, incl. patients with IMP dose reduction	72.2	37.5	34.6 (11.3, 57.9)	0.0018
Key secondary efficacy endpoint - Proportion of patients with mean IGF-1≤ULN at Week 22 and Week 24 and mean GH cycle <2.5 ug/L at Week 24	70.0	37.5	32.3 (8.8, 55.7)	0.0035



Press release-Camurus, 20 June 2023

Significant improvement in patient's QoL

AcroQoL	Treatment arm	LS Mean of Change from Baseline	p-value
Total Score	CAM2029	4.685 (1.510, 7.861)	0.0038
	Placebo	2.237 (-2.246, 6.721)	0.3280
Physical Domain Score	CAM2029	3.968 (0.346, 7.590)	0.0318
	Placebo	-1.198 (-6.348, 3.952)	0.6484
Psychological Domain Total Score	CAM2029	5.054 (1.684, 8.424)	0.0033
	Placebo	4.433 (-0.313, 9.178)	0.0671



Press release-Camurus, 20 June 2023

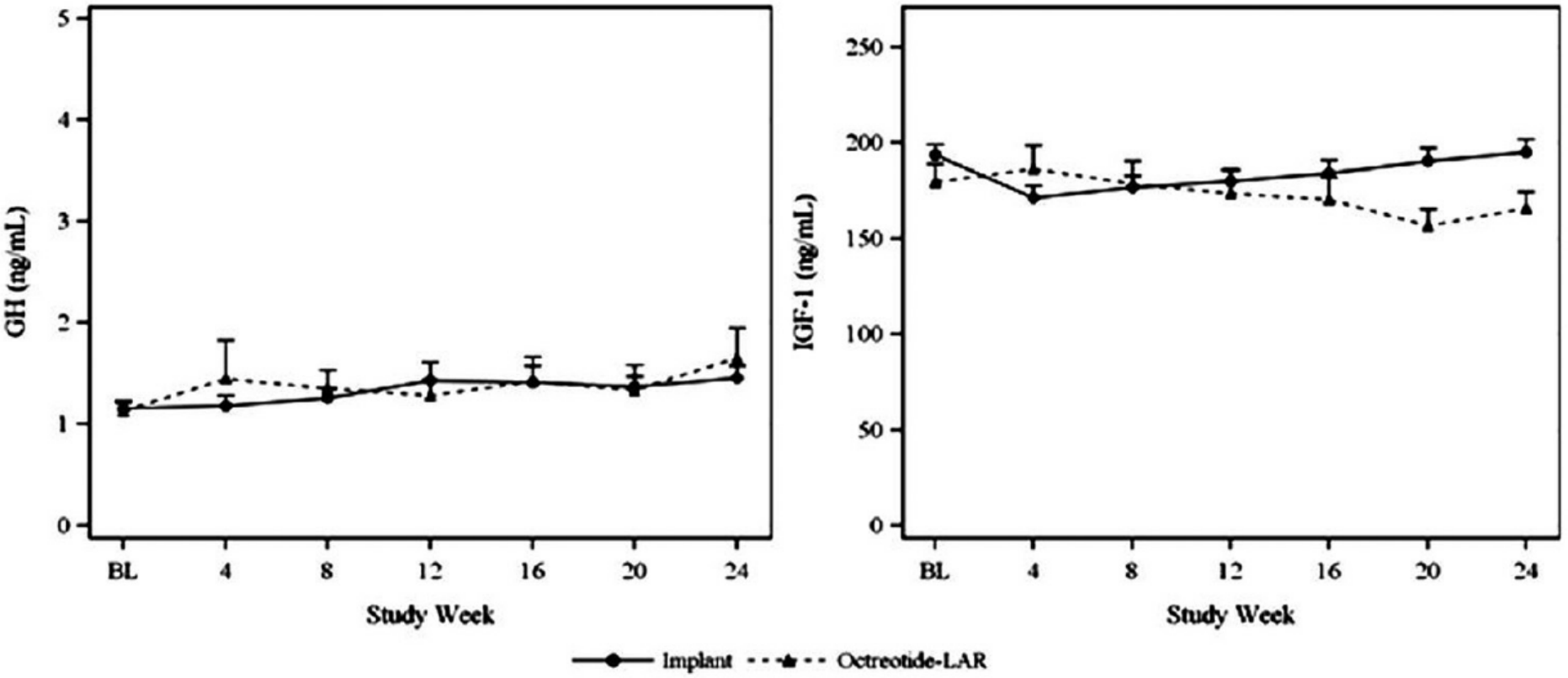
Somatoprim (DG3173-PTR3173)

- High affinity to **SSRT 2,5,4**
- Highly **selective** for suppressing GH
- **Absence** of inhibitory effect on insulin secretion
- **Similar GH-suppression** in GH-secreting adenomas to that of OCT
- Positive response is more likely in "**sparsely granulated**" than in "densely granulated" tumors
- Not yet available commercially

European Journal of Endocrinology (2012) 166 223–234

OCT Implant (VP-003)

Efficacy and Safety of an Octreotide Implant



N:163

On OCT >3mo

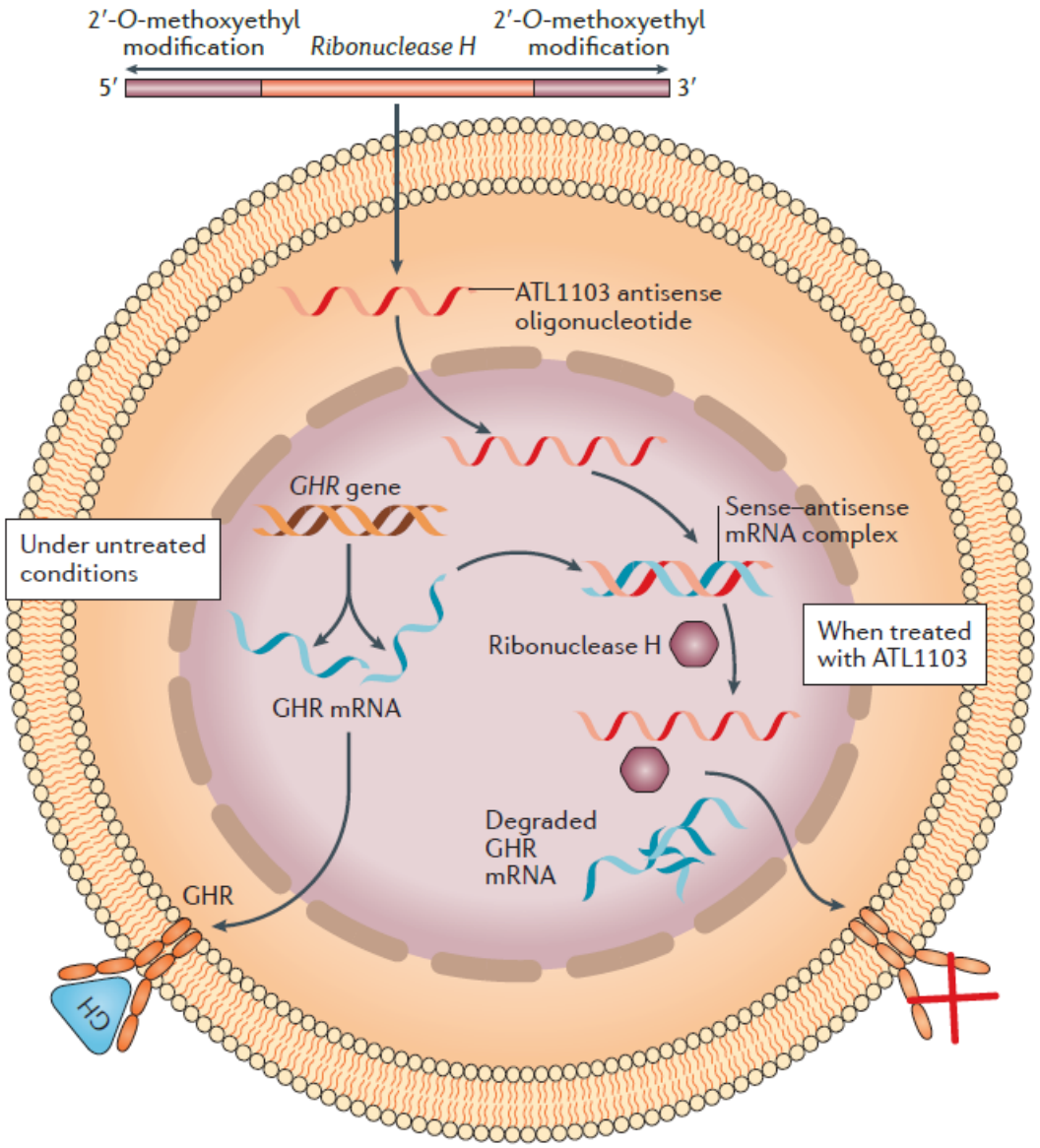
Success rate in maintenance of NL IGF-1 **AND** GH<2.5 ng/ml: **86**%vs 84%

J Clin Endocrinol Metab, October 2013, 98(10):4047–4054

Antisense oligonucleotide

Cimdelirsen

ATL-1103



European Journal of Endocrinology **(2018) 179, 97–108**

Cimdelirsen

- Once monthly sc administration
- Significant dose-dependent reduction in GHBP (a biomarker of GHR)
- Significant reduction in IGF-1
- No increase in fasting GH level
- Good safety and toleribity
- Improvement in QoL score

J Endocrine Soc, Volume 6, Issue Supplement_1, November–December 2022

Available Medications

Somatostatin Analogs

Octreotide **Lanreotide**
Pasirotide

Dopamine Agonists

Cabergulin

GH-Receptor Blockers

Pegvisomant

Novel medications

Somatostatin Analogs

Oral octreotide

Somatropim (DG1373)

CAM2029 (sc)

Octreotide implant

GHR-antagonists

Cimdelirsen

ATL-1103

Thanks for your attention