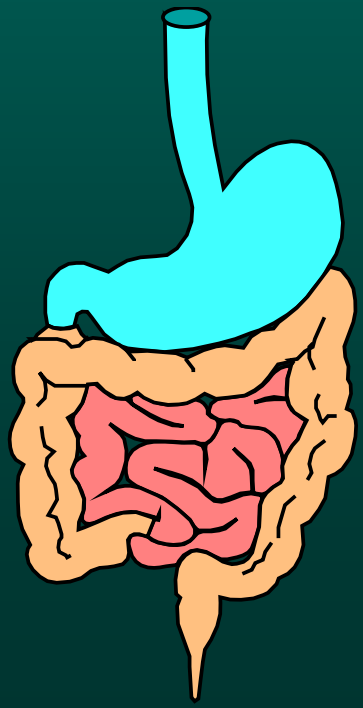
Sandostatin LAR

Use in GEPET



Types of GEPET

- VIPoma*
- Carcinoid tumor*
- Gastrinoma
- Insulinoma
- Glucagonoma
- GRFoma
- Somatostatinoma

* = Approved indication for Sandostatin and Sandostatin LAR in Canada

VIPoma

- Major peptide/hormone
  - VIP
- Syndrome/symptom
  - Verner-Morrison syndrome or pancreatic cholera syndrome (watery diarrhea, hypokalemia and achlorhydria)
  - Hypercalcemia, glucose intolerance and flushing
- Percent malignant
  - 80
- Main sites (%)
  - Pancreas (90); Adrenal (10%)

Ultimate Goals for the Treatment of Neuroendocrine Tumours

- Total eradication by surgery *(not possible in most cases)*
- Abrogation of tumour growth and/or amelioration of clinical symptoms
- Improving and maintaining a good quality of life

Carcinoid Tumour

- Major peptide/hormone
  - Serotonin
- Syndrome/symptom
  - Carcinoid syndrome
    - diarrhea, flushing - most common
    - endocardial fibrosis, respiratory complications, pellagra, and arthropathy and myopathy
- Percent malignant
  - 2-60 (site-dependent metastases)
- Main sites (%)
  - Appendix (40); small intestine (27); rectum (13); bronchus (11.5)

Incidence

Carcincoid Tumours	1: 150 000
Gastrinoma	1: 1 000 000
Insulinoma	1 : 1 000 000
Glucagonoma	1: 20 000 000
VIPoma	1: 10 000 000
Somatostatinoma	1: 40 000 000

Treatment of GEPET

Types of Treatments for GEPET

- Surgery
- Liver dearterialization
- Irradiation
- Medical Therapy
  - Chemotherapy
  - Somatostatin analogues
  - Interferon

Mechanism of Action of Sandostatin

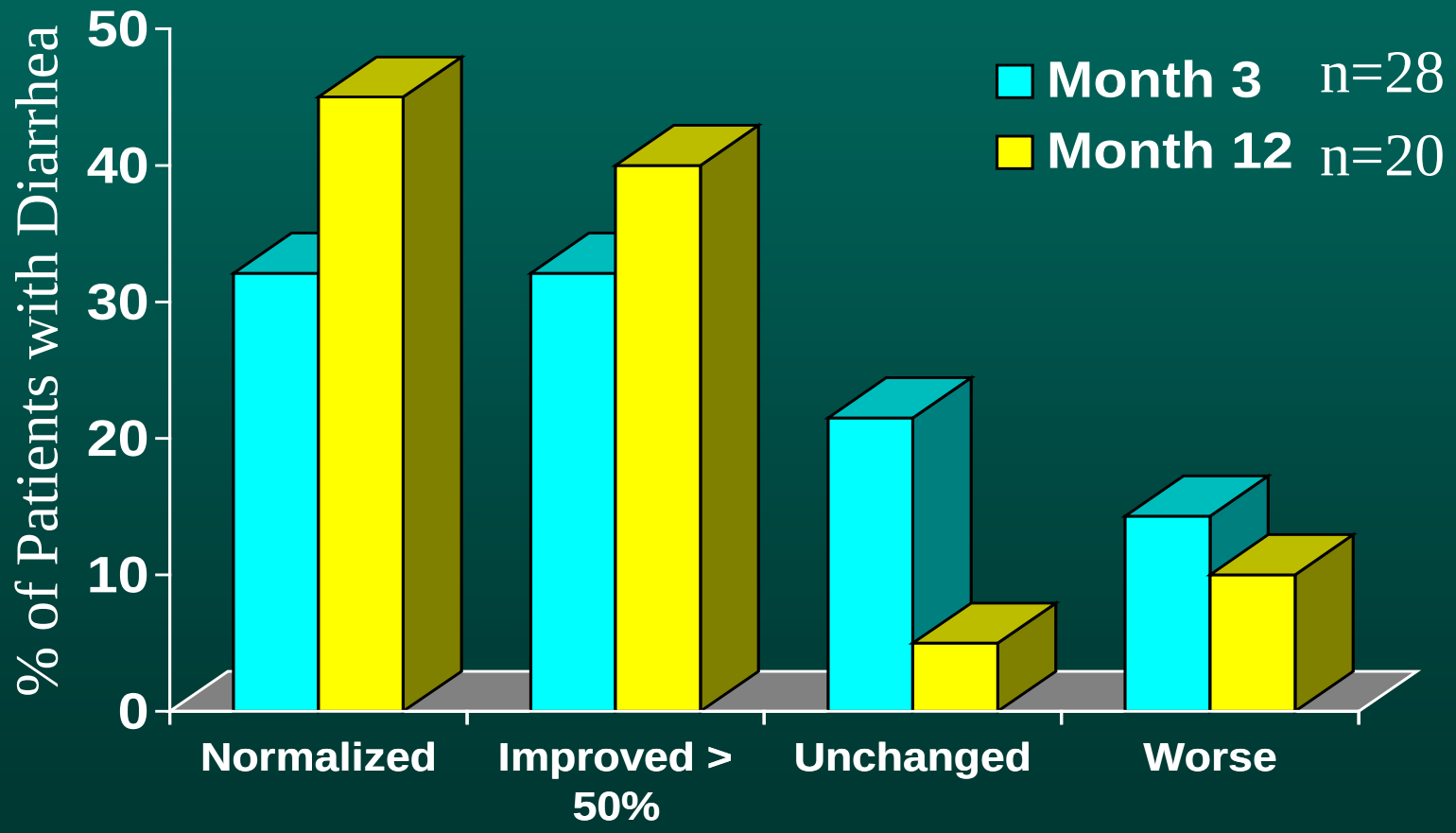
- Suppress the release of peptides and amines from the tumors
- Inhibit the actions of these mediators on target tissues
- Affect tumour growth?

Carcinoid Syndrome
(approved in Canada)

- Response rates are generally between 60-100%
- Control of diarrhea is usually accompanied by
  - increase in appetite and weight gain
  - increase in Karnofsky performance score
  - improved quality of life
- Life-saving effect in reversing carcinoid crisis have been documented by several investigators
- Reduces urinary 5-HIAA excretion (doesn't always predict response to treatment)

Sandostatin in Carcinoid Syndrome

Diarrhea

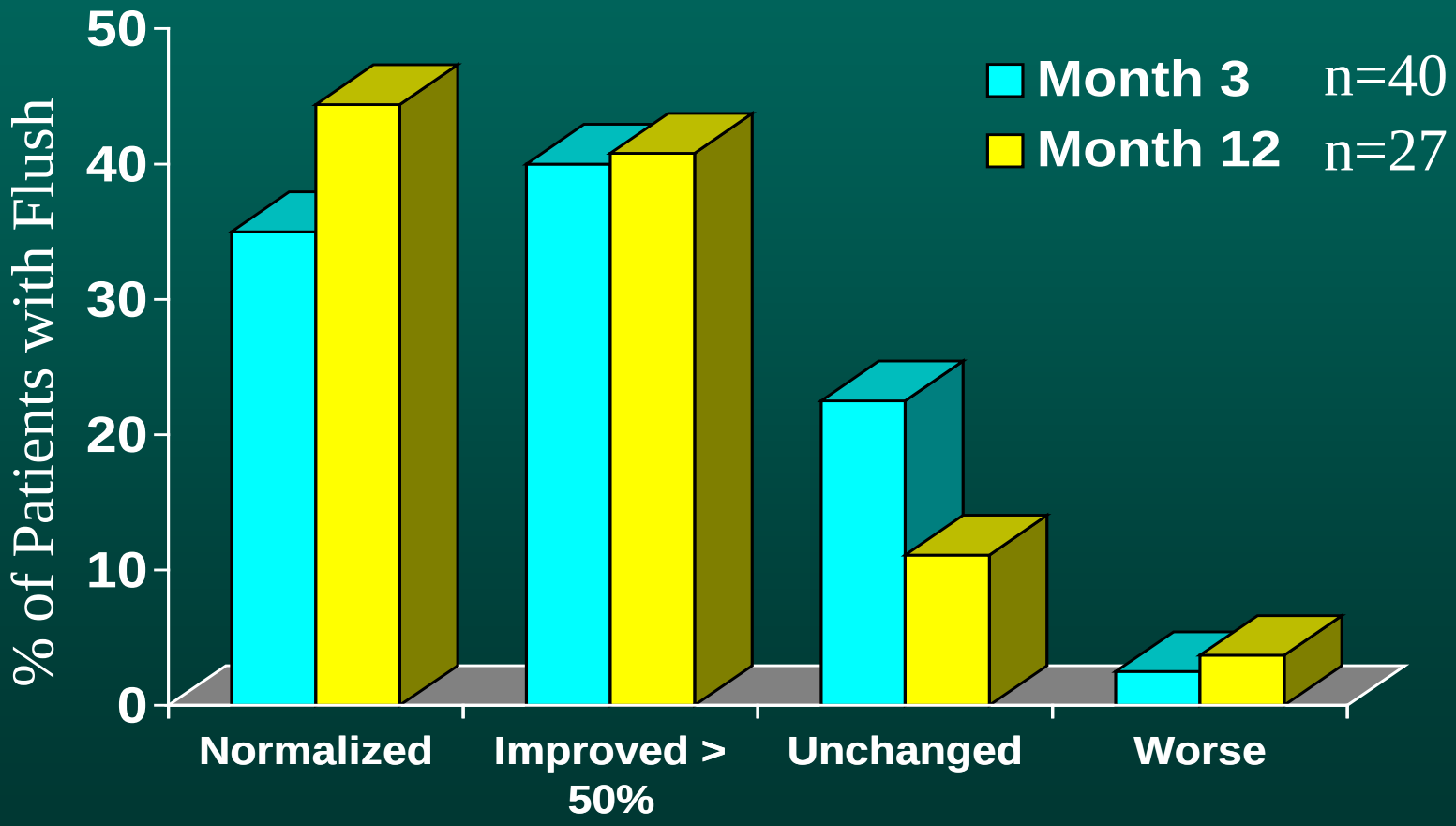


Octreotide 200-500 µg TID

Arnold *et al*. Gut, 38:430-438, 1996

Sandostatin in Carcinoid Syndrome

Flush



Octreotide 200-500 µg TID

Arnold *et al*. Gut, 38:430-438, 1996

VIPoma
(approved in Canada)

- Sandostatin provides rapid short- and long-term control of diarrhea in approximately 70-100% of patients
- Reduces plasma VIP concentrations in approximately 60-89% of patients
- Weight gain often accompanies control of diarrhea
- Quality of life can be improved with relief of symptoms

Octreotide Acetate Long-Acting Formulation Versus Open-Label Subcutaneous Octreotide Acetate in Malignant Carcinoid Syndrome

Rubin J *et al.* Journal of Clinical Oncology
Vol 17, No. 2:600-606, 1999

Octreotide LAR vs SC in Carcinoid Syndrome
(Protocol Design)

93 patients with carcinoid syndrome due to a carcinoid tumor

Double-blind for octreotide LAR and open-label for sc, randomized (after 2 week screening with sc Sandostatin, followed by 3-5 day washout)

LAR 10mg | **LAR 20mg** | **LAR 30mg** | **SC 0.3-0.9 mg/d**

The primary efficacy endpoint was treatment response. Other efficacy endpoints were daily stool frequency, flushing episodes, rescue medication and 5-HIAA levels.

Study Objectives

Primary

- Compare once-monthly IM Sandostatin LAR to Sandostatin for control of diarrhea and flushing associated with carcinoid syndrome

Secondary

- Evaluate safety and tolerability of Sandostatin LAR
- Assess 5-HIAA urinary excretion as biological indicator of response
- Measure octreotide levels at 10-, 20-, and 30-mg doses of Sandostatin LAR

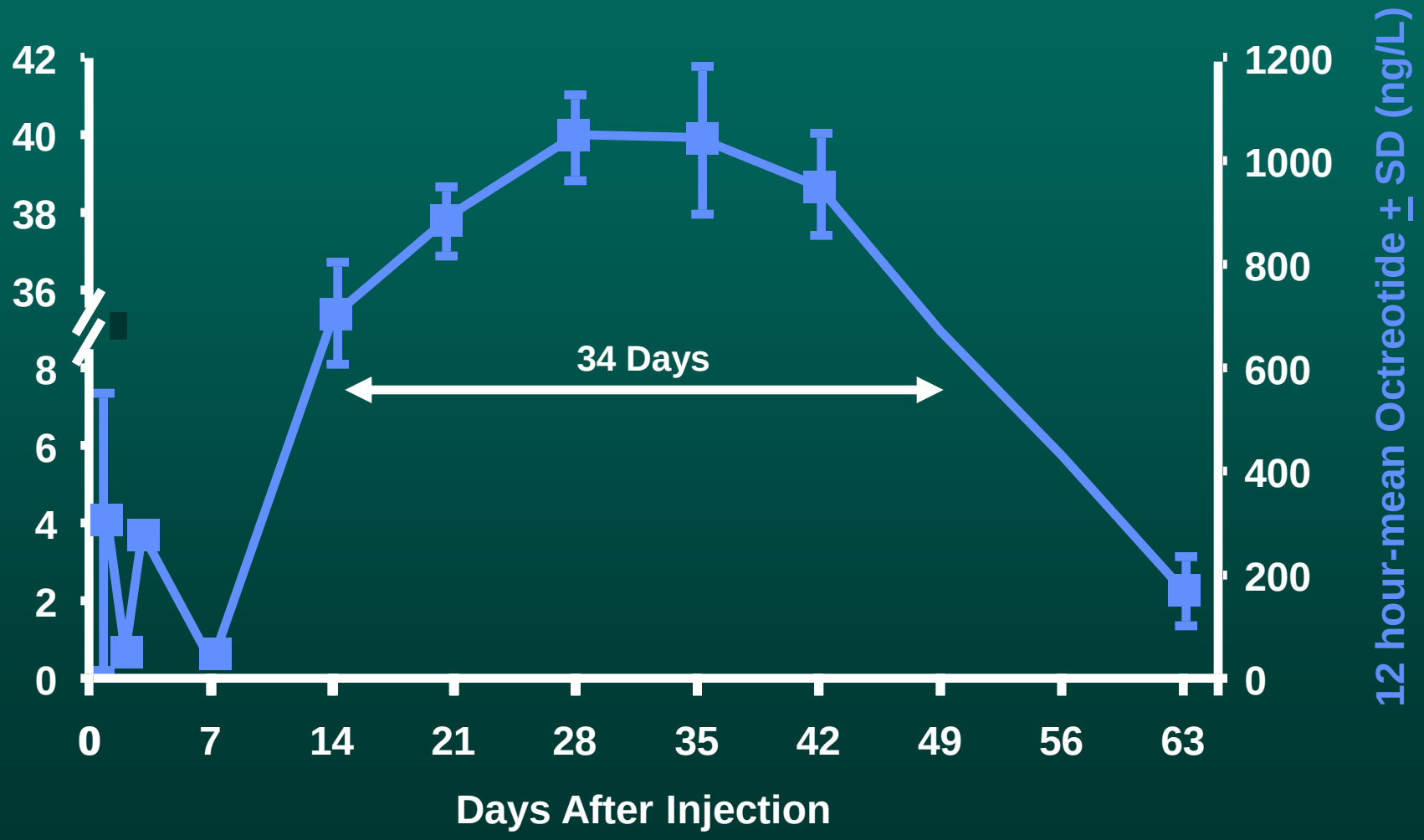
Octreotide LAR vs SC in Carcinoid Syndrome

Study Design

- Patients experienced control of symptoms with sc
- Continued to show symptom control for at least a 2-week screening period
- Washout period of 3-5 days
- Patients then randomly assigned to receive one of the four treatments
  - LAR 10, 20 or 30 mg or sc at the same dose as screening
- Assignment to LAR was double-blind
- All patients received LAR on day 1, but continued to receive concomitant sc every 8 hours at the previous dose

Serum Octreotide and GH Concentrations After Sandostatin LAR Injection

Mean Serum Octreotide and GH Concentrations After Injection of a Single 30-mg Dose in a Typical Patient



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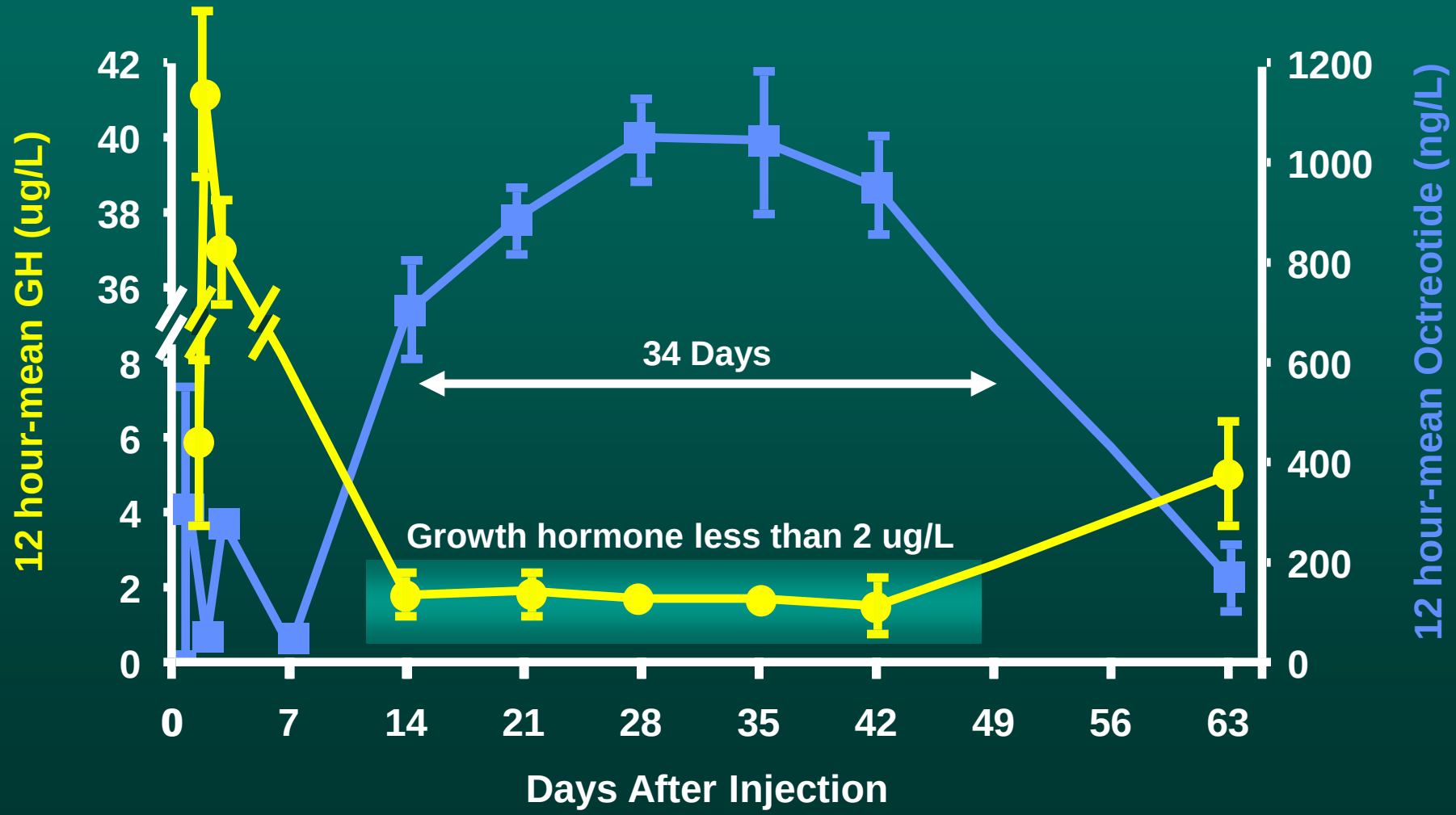


Lancranjan, et al. *Metabolism.* 1996. Grass, et al. *Metabolism*. 1996.

Patients

- Histologically, confirmed carcinoid tumor with carcinoid syndrome
- Symptoms of flushing and diarrhea had to have been well controlled by sc
  - two or fewer flushing episodes per day
  - average stool frequency of three of fewer per day (maximum of five stools on any one day)
- For patients efficacy to be assessable, symptoms must have returned during the washout period
  - three episodes of flushing in a single day and/or
  - an increase of at least tow stools daily for consecutive days above prewashout average

Procedures

- Patients receiving LAR who lost symptom control could use rescue sc until symptom were controlled to screening frequency
  - increased stool frequency by at least 2 per day for 2 consecutive days or flushing frequency increased to at least three episodes per day for 1 day
- Patients taking sc who required rescue could increase dose by 50%; patients on LAR - same dose used before washout
- After relief was achieved for 24 hours, d/c
- Rescue could be repeated a second time
- If first two episodes required more than 5 days total or if a third rescue episode was needed, patients received sc until the next visit.

Efficacy and Safety Assessments

- Primary efficacy assessment was treatment response
- Efficacy assessments included the daily frequency of stools and flushing episodes, number of patients using rescue medication, and 24-hours urinary 5-HIAA concentrations
- Number of safety assessments

Definition of Treatment Response

Complete success	• No supplemental medication (Sandostatin) needed
Partial success	• Supplemental medication needed on no more than 2 occasions or for not more than 5 days
Treatment failure	• Supplemental medication needed on 3 or more occasions or for 5 days or more days

Statistical Analysis

- Because of the low natural incidence of the carcinoid syndrome, only a limited number of patients were expected
- Consequently, the study was designed to look at the equivalence between the sc and LAR formulations and not to detect statistically significant differences among groups!!!!
- Conclusions were based on clinical rather than statistical findings

Results

Patient Demographics and Clinical Characteristics

- 93 patients constituted the intent-to-treat population
- 79 patients constituted the efficacy-assessable population
  - 9 patients discontinued before week 24
  - 5 patients finished study but were later found not to have met the necessary inclusion criteria
- Demographic and clinical characteristics were comparable except for age
  - median age of patients in the 20-mg group was younger

Discontinuations, Deaths, and Serious Adverse Events

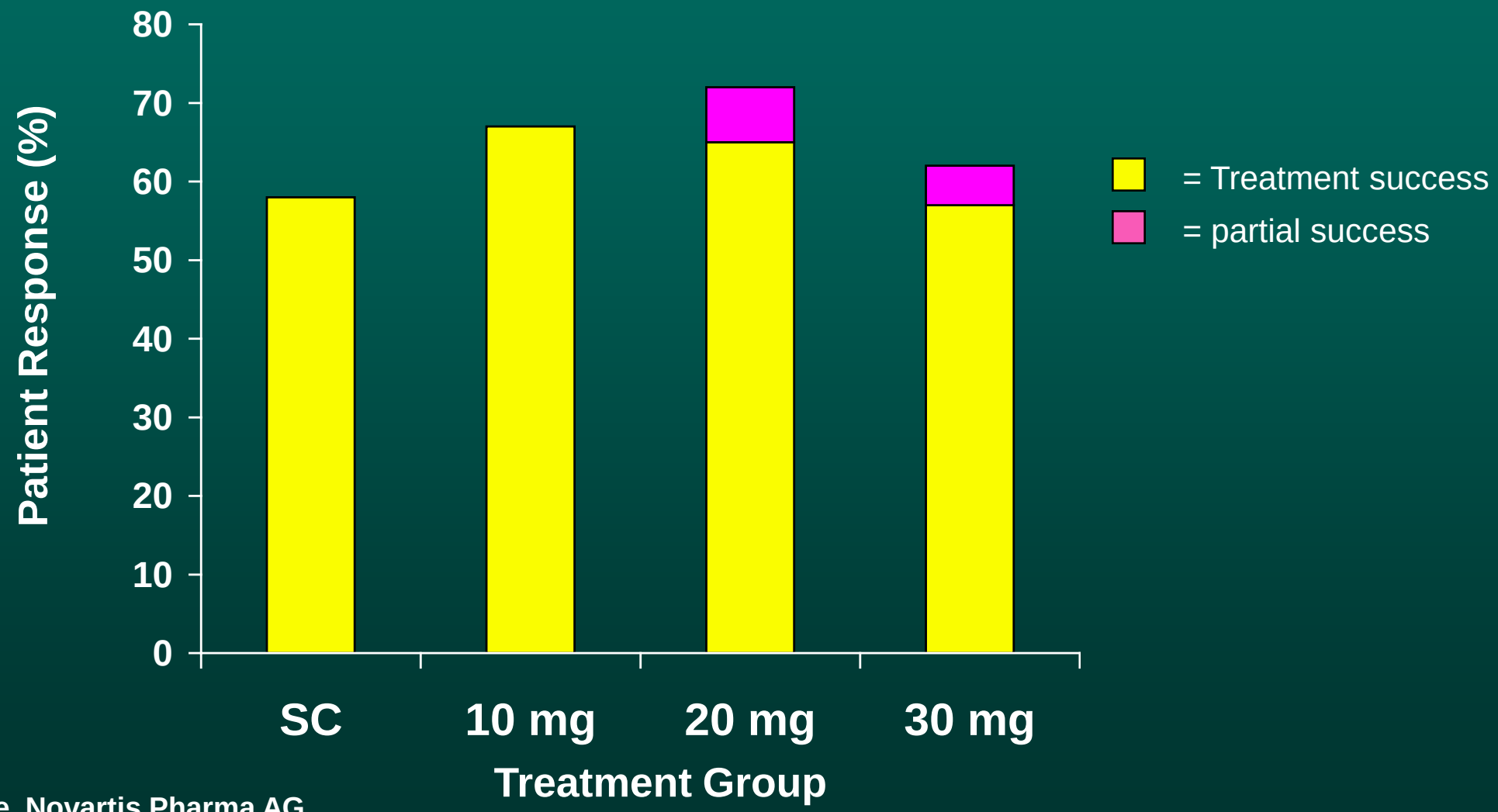
Cause	Number of Patients
Discontinuations	13
Consent withdrawal	2
Failure to return	4
Adverse event	1
Treatment failure	2
Death	3
Unknown	1
Deaths	
Renal failure/hypotension/hypoglycemia	1†
Respiratory distress	1‡
Pulmonary embolism	1‡
Serious adverse events	17

Data on file, Novartis Pharma AG.

† 20-mg LAR group; ‡ 30-mg LAR group.

Treatment Response

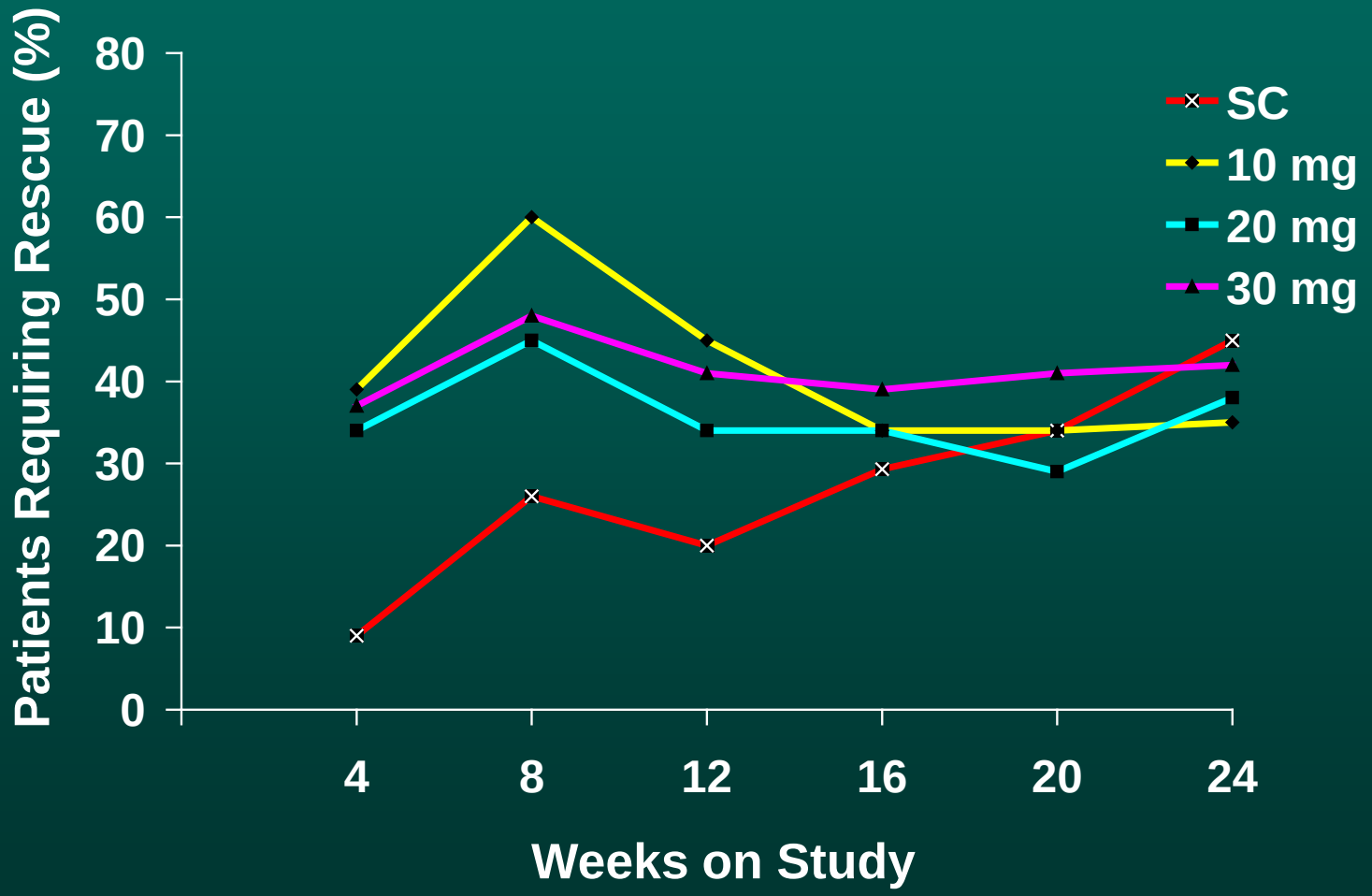
Percentage of Patients (Efficacy-Evaluable Population) With Treatment Success and Partial Treatment Success at Week 20 and/or Week 24 by Treatment Group



Data on file, Novartis Pharma AG.

Supplemental Medication Required

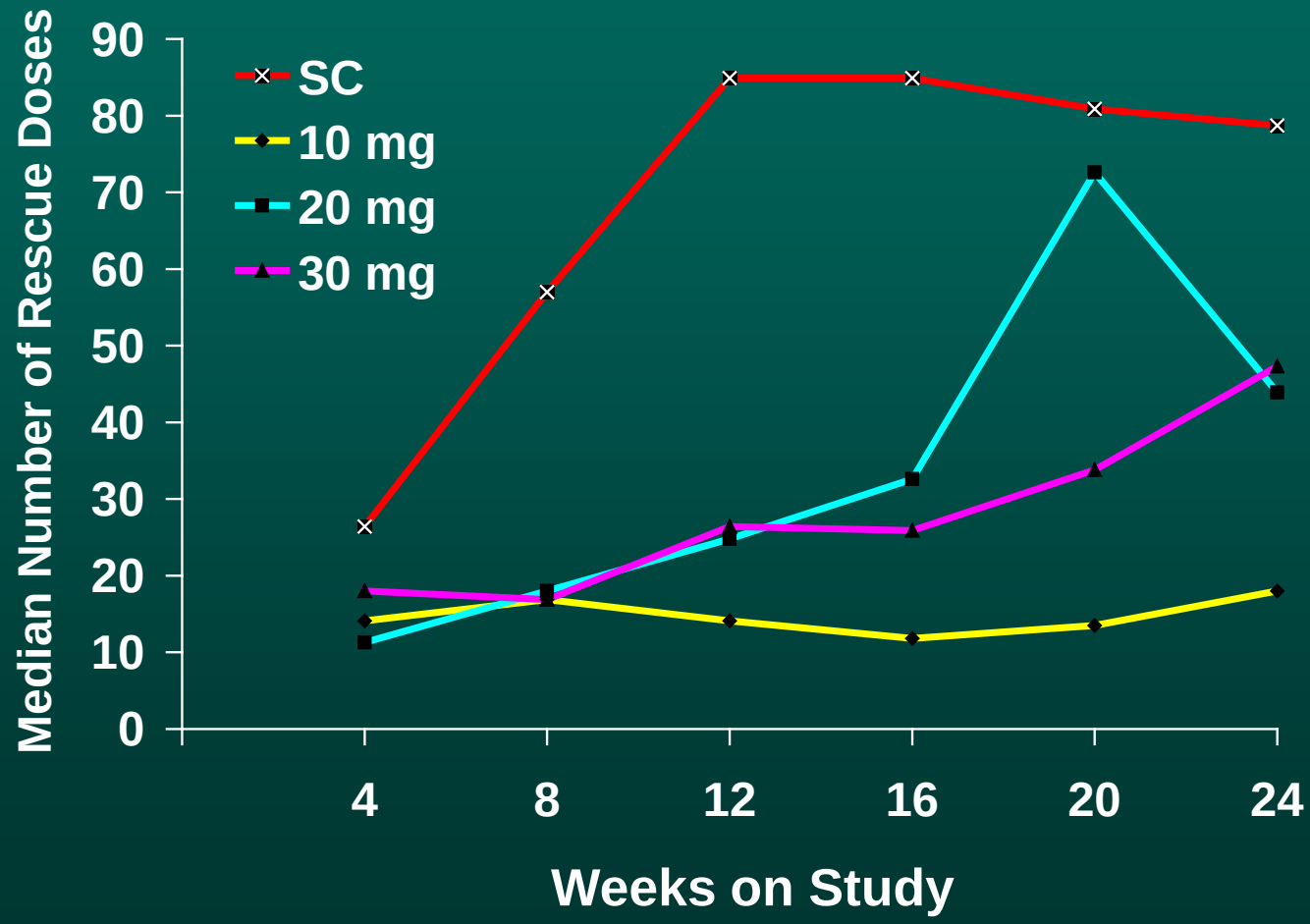
Percentage of Patients (Efficacy-Evaluable Population) Requiring Supplemental Medication in Each Treatment Group During the 24-Week Treatment Period



Data on file, Novartis Pharma AG.

Supplemental Medication Required

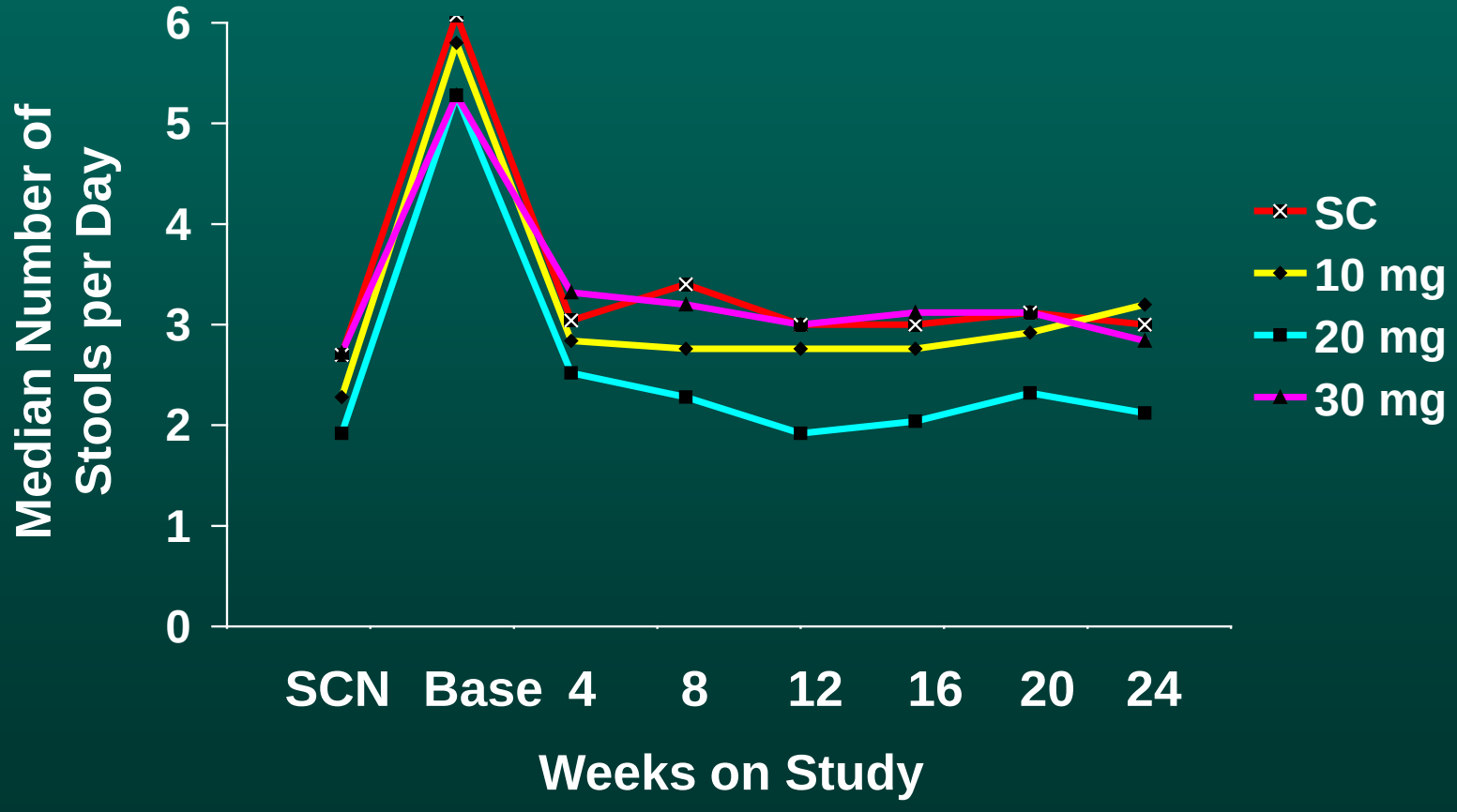
Median Number of Supplemental SC octreotide Doses Taken by Patients (Efficacy-Evaluable Population) Requiring Rescue During the Preceding 4-week Interval by Treatment Group.



Data on file, Novartis Pharma AG.

Symptomatic Control of Diarrhea

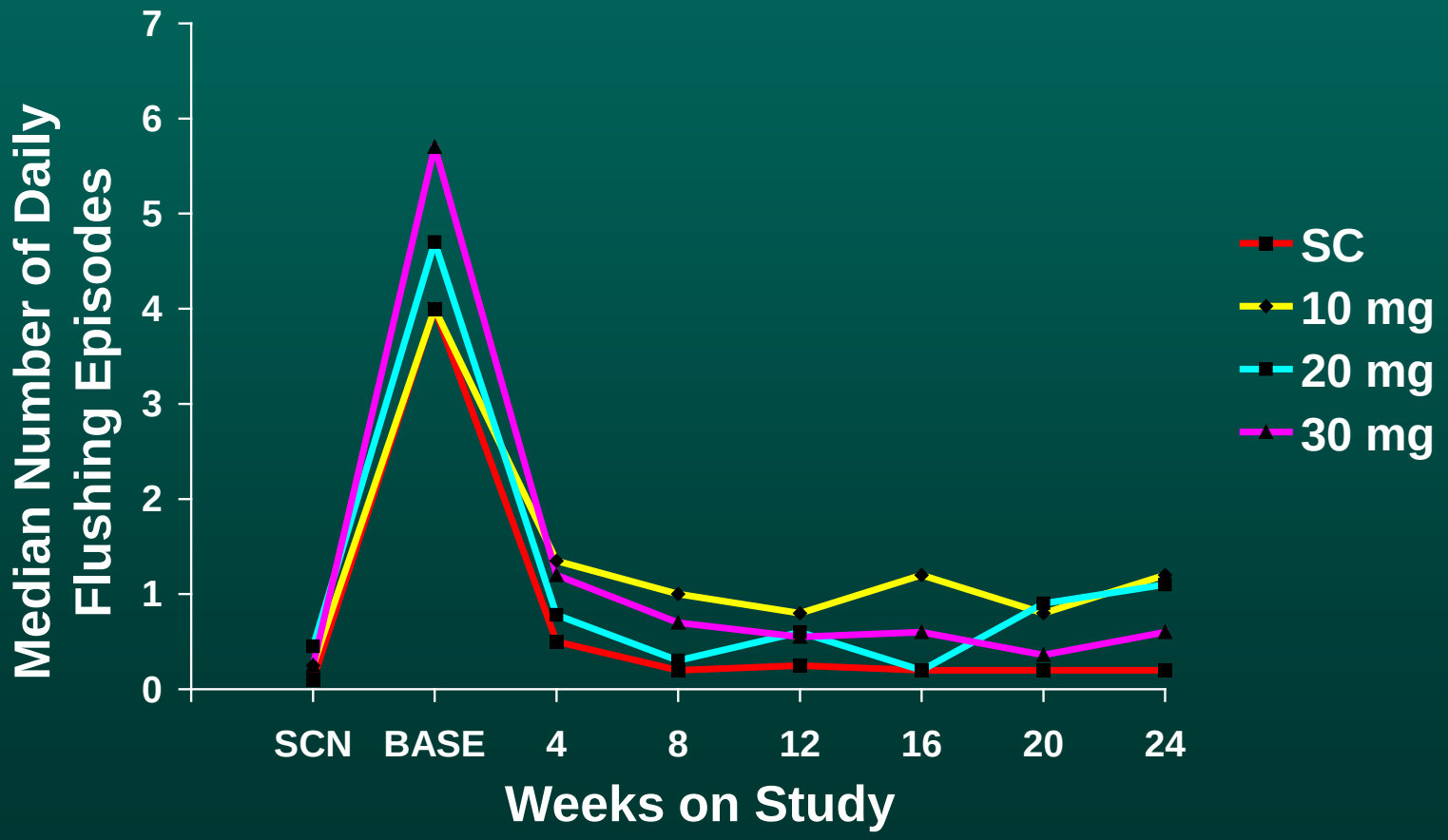
Median Number of Stools per Day in 47 Efficacy-Evaluable Patients Throughout Screening (SCN), Baseline (BASE), and 24-Week Treatment Period by Treatment Group



Data on file, Novartis Pharma AG.

Symptomatic Control of Flushing

Median Number of Flushing Episodes per Day in 33 Efficacy-Evaluable Patients Throughout Screening (SCN), Baseline (BASE), and 24-Week Treatment Period by Treatment Group



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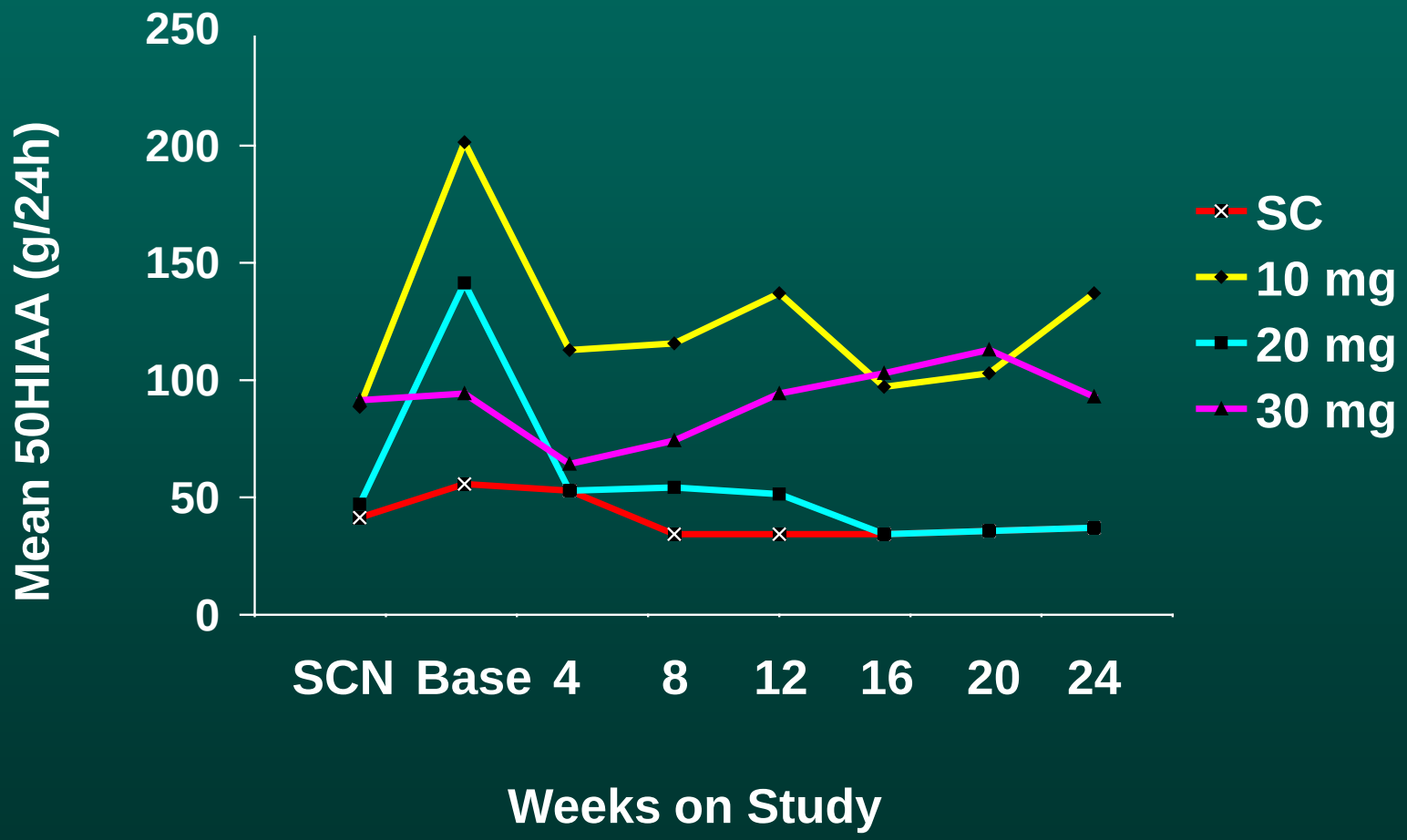
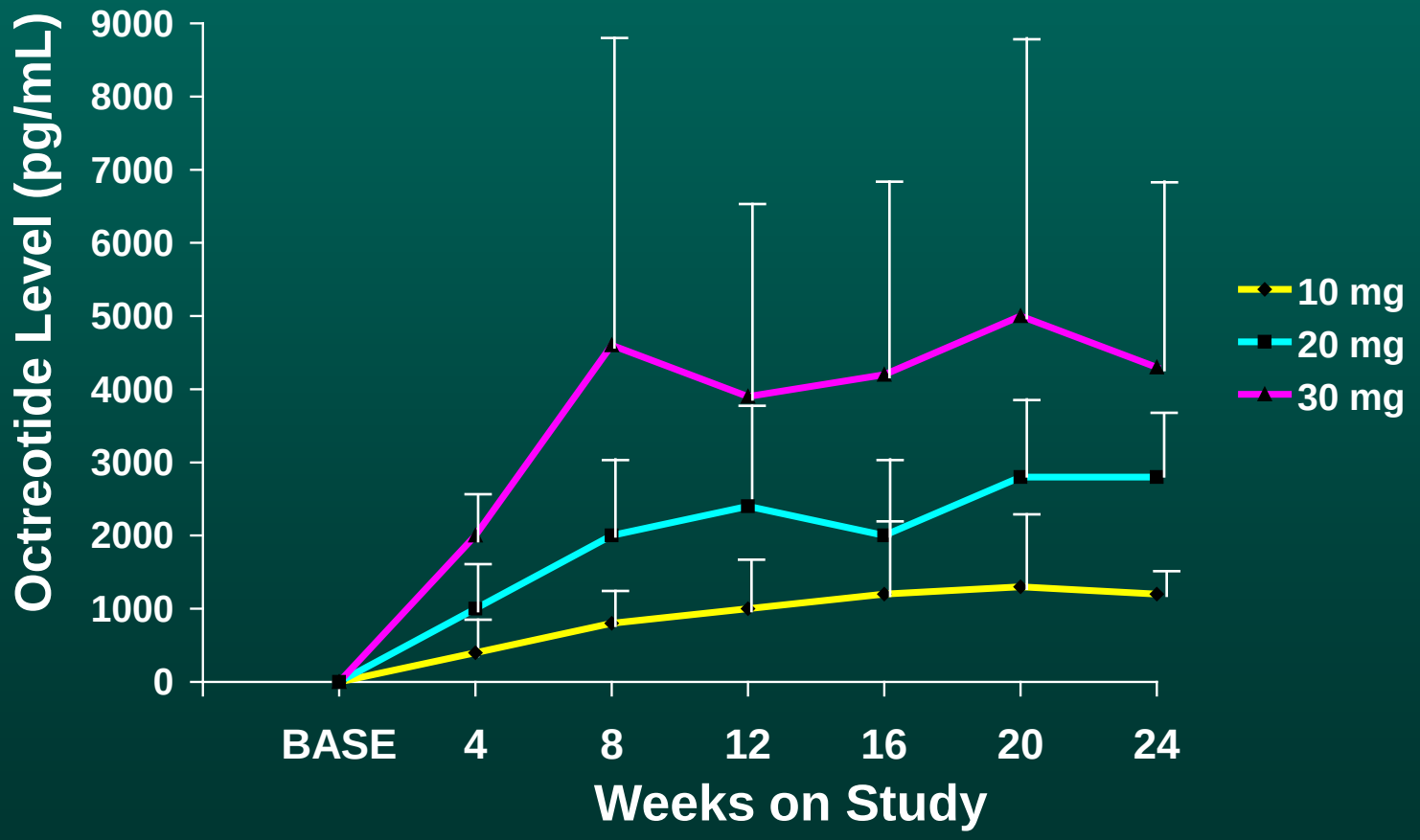
Urinary 5-HIAA Excretion



Data on file, Novartis Pharma AG.

Pharmacokinetics of Sandostatin LAR

Mean Serum Octreotide Concentration (pg/mL) (Efficacy-Evaluable Population) After IM Administration of Sandostatin LAR at 10 mg (n=16), 20 mg (n=13), or 30 mg (n=19) Every 4 Weeks.



*** Baseline levels > 160 pg/mL or 0 pg/mL were excluded. Data on file, Novartis Pharma AG.**

Treatment-Related Adverse Events

Adverse Event	Sandostatin (n=26)	Sandostatin LAR 10 mg (n=22)	Sandostatin LAR 20 mg (n=20)	Sandostatin LAR 30 mg (n=25)
Injection site inflammation	1	0	0	1
Injection site reaction	0	0	1	0
Asthenia	0	1	0	0
Fever	0	1	0	0
Hypothyroidism	0	0	1	0
Abdominal pain	1	0	0	0
Flatulence	1	0	0	1
Nausea	1	1	1	0
Steatorrhea	0	0	0	1
Cholelithiasis	2	1	1	1
Rash	0	0	2	0
Taste perversion	0	1	0	0
Renal calculus	0	0	0	1

Data on file, Novartis Pharma AG.

Newly Occurring Gallbladder Abnormalities

Adverse Event	Sandostatin (n=26)	Sandostatin LAR 10 mg (n=22)	Sandostatin LAR 20 mg (n=20)	Sandostatin LAR 30 mg (n=25)
Gallstones	1	2	0	2
Sludge	0	2	0	0
Dilatation of ductal system	0	3	0	1

Data on file, Novartis Pharma AG.

Sandostatin LAR — Dosing Algorithm

Test dosing of subcutaneous Sandostatin for 2 weeks. Immediately after last subcutaneous injection, assess side effects, rule out acute toxicity, and verify symptom response

Switch to Sandostatin LAR Intragluteal injection 20 mg q 28 days (No washout period)

+

Continue sc Sandostatin for 2 weeks while awaiting the therapeutic level of the first injection of Sandostatin LAR

Evaluate after 2 months

Symptoms controlled

Symptoms not controlled

Consider trial period at 10 mg q 28 days. If symptoms recur, increase dose to 20 mg q 28 days

Maintain dose at 20 mg q 28 days

Increase dose to 30 mg q 28 days

Summary

- Sandostatin LAR provides efficacy, safety, and tolerability comparable to Sandostatin with the benefit of a once-monthly injection.
- A 20-mg initial dose is recommended.
- Monthly injections are preferred by patients and should increase compliance.