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Welcome to R&D Day

November 16, 2017, New York, NY

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R&D Day

Peter Greenleaf

Chairman and Chief Executive Officer

Sucampo Pharmaceuticals, Inc.

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Agenda for Today

Welcome
Peter Greenleaf

Speaker Introductions
Dr Peter Kiener

Familial Adenomatous Polyposis & CPP-1x/Sulindac
Drs Carol Burke and Peter Kiener

Niemann-Pick Type-C & VTS-270
Drs Paul Gissen, Dan Ory, and Peter Kiener

Q&A Session

Lunch & Discussion

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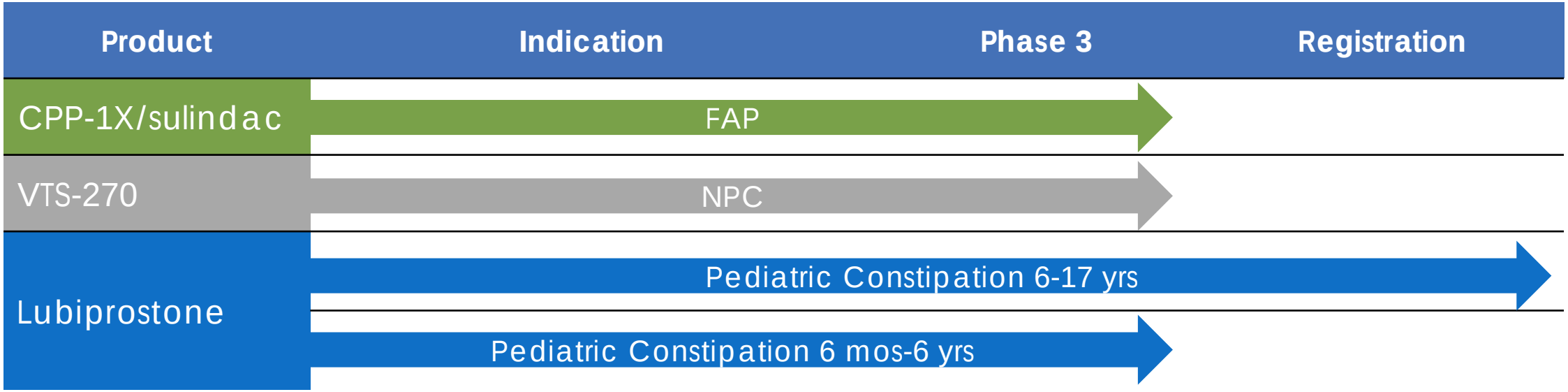
Speaker Introductions

Peter Kiener, D. Phil

Chief Scientific Officer

Sucampo Pharmaceuticals, Inc.

Diversified and Late-stage Portfolio



Carol Burke, MD, FACG, FACP, FASGE, AGAF

Director of the Section of Polyposis at the Sanford R Weiss MD Center for Hereditary Colorectal Neoplasia and Vice Chair of the Department of Gastroenterology and Hepatology at the Cleveland Clinic in Cleveland, Ohio.

Paul Gissen, MBCHB PhD

Professor of Metabolic Diseases at University College of London and Consultant in Paediatric Metabolic Diseases at Great Ormond Street Hospital for Children in London, UK.

Dan Ory, MD

Professor of Internal Medicine, Cell Biology, and Physiology; Co-Director, Diabetic Center for Cardiovascular Disease; Alan A. and Edith L. Wolff Distinguished Professor of Medicine at the Washington University School of Medicine.

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Familial Adenomatous Polyposis (FAP)

Carol A. Burke, MD, FACG, FACP, FASGE, AGAF

Director of the Section of Polyposis

Sanford R Weiss MD Center for Hereditary Colorectal Neoplasia

Vice Chair of the Department of Gastroenterology and Hepatology

Cleveland Clinic, Cleveland, Ohio

Our Discussion Today - Familial Adenomatous Polyposis (FAP)

- What is FAP?
- The Science of FAP
- CPP-1X/ Sulindac Program
- A PATIENT'S STORY
- How Is FAP Managed Today?
- SUMMARY

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What Is FAP?

An Introduction

FAP: Inheritance, Natural History, Epidemiology

FAP is a genetic, autosomal dominant disease caused by a mutation in the adenomatous polyposis coli (APC) gene on chromosome 5 (5q21)[1]

FAP is a rare, life-threatening disease characterized by 100s to 1000s of colorectal adenomas & if left untreated, there is a 100% lifetime risk of developing colorectal cancer (CRC)[2]

In the US, FAP affects 1 in 10,000 people; life expectancy is 40 years if colectomy is not performed[3]

1. Kinzler KW, et al. *Science.* 1991;253:661-665; 2. Septer S, et al. *Fam Cancer.* 2016;15:447-485; 3. Nugent KP, et al. *Dis Colon Rectum*. 1993;36:1059-1062.

FAP Impacts Lower Digestive Tract & Beyond

Colon/rectum

- 100s to 1000s of colorectal adenomas
- Untreated, there is a 100% lifetime risk of colon cancer

Stomach

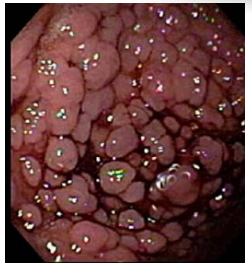
- ~100% of patients develop fundic gland polyps; many are dysplastic
- ~2% of patients develop stomach cancer from dysplastic polyps
- ~5% of patients develop gastric adenomas

Duodenum

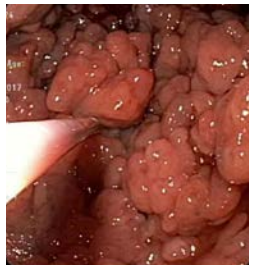
- ~100% of patients develop adenomatous duodenal polyps
- ~3-36% develop duodenal cancer, depending on the polyposis stage

Desmoids

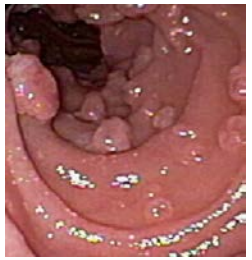
- Occur in ≥10–25% of patients
- ~10% of patients have severe complications from tumor growth
- Second leading cause of death in FAP



Colonic features



Stomach features



Duodenum features

Kennedy RD, et al. *J Pediatr Surg.* 2014;49:82-86; Samarasinghe M, Hawkins J. *Gastrointestinal Nursing.* 2014;12:Epub; Septer S, et al. *Fam Cancer.* 2016;15:477-485; Vasen HF. *Gut.* 2008;57:704-713; Waller A, et al. *J Pediatr Genet.* 2016;5:78-83. Photos courtesy of Carol Burke, MD.

FAP Impacts Lower Digestive Tract & Beyond

Bone and skin

- ~50-90% of patients develop osteomas
- 50% of patients develop epidermoid cysts

Other organs/structures

- ~70-80% of FAP patients develop asymptomatic bilateral congenital hypertrophy of the retinal pigmented epithelium (CHRPE)
- ~11-27% of patients have supernumerary teeth

Other malignant lesions

- ~2-3% of FAP patients will develop thyroid cancer
- ~1% of pediatric patients will develop hepatoblastoma
- <1% of patients will develop brain tumors

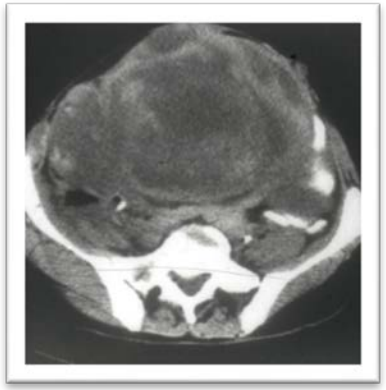
"With improvements in early recognition of colorectal polyposis, colectomy preventing colorectal adenocarcinoma, & the increased awareness of the need for surveillance endoscopy after colectomy, *extracolonic manifestations of the disease are becoming the leading causes of death in FAP* & thus require careful surveillance."

Septer S, et al. 2016

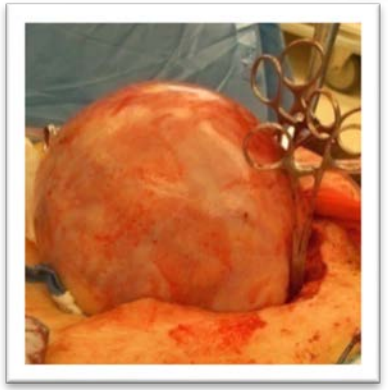
Kennedy RD, et al. *J Pediatr Surg.* 2014;49:82-86; Samarasinghe M, Hawkins J. *Gastrointestinal Nursing.* 2014;12:Epub; Septer S, et al. *Fam Cancer.* 2016;15:477-485; Vasen HF. *Gut.* 2008;57:704-713; Waller A, et al. *J Pediatr Genet.* 2016;5:78-83.

Extra-intestinal Features of FAP

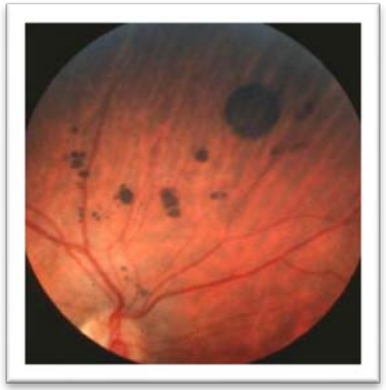
- Desmoid tumors (15%)
- Thyroid carcinoma (2-17%)
- Adrenal adenoma (7-13%)
- Osteomas (50-90%)
- Supernumerary teeth (11-27%)
- CHRPE (70-80%)
- Soft tissue tumors (50%)
  - Lipoma, fibroma, sebaceous cysts
- Hepatoblastoma (<2%)



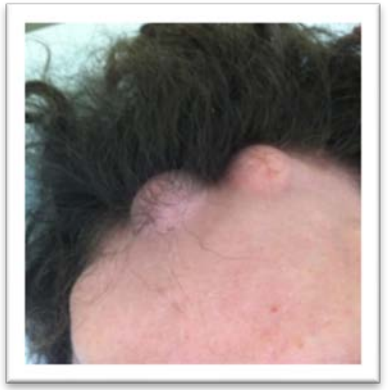
CT scan of desmoid tumor



Surgical removal of desmoid tumor



CHRPE of the retina



Osteomas on the forehead

Eponyms; Gardner's syndrome (extra intestinal manifestation); Turcot's syndrome (medulloblastoma, glioma). Desmoid tumor photos courtesy of James Church, MD; Osteoma photo courtesy of Carol Burke, MD.

FAP Negatively Affects Psychosocial Well-Being

Systematic review (1986-2007) identified studies focused on FAP impact on psychosocial well-being (Douma et al. 2008)

STUDY	PATIENTS	RESULTS
Miller et al. 1986	Post-surgery chemoprevention trial	• Reactions to diagnosis: anger, anxiety, fear of death • 77% felt guilty about passing FAP to their children • Perceived disfigurement inversely correlated with well-being
Andrews et al. 2006	At risk for & with FAP	• Moderate-to-high support needs for managing worry for their children and fear of cancer • 77% received FAP information from relatives despite a preference to be informed by medical experts • 16% reported feeling discriminated against, especially at work
Douma et al. 2010	Age ≥16 with FAP, at risk for inheriting FAP or non-carrier	• Surgically treated patients had poor HRQOL • Post-surgery patients had negative body image & poor social functioning • In 41%, FAP affected their employment status

Miller HH, et al. *Int J Psychiatry Med.* 1986;16:211-230; Andrews L, et al. *Genet Med.* 2006;8:697-703; Douma KFL, et al. *Colorectal Disease.* 2010;13:669-677.

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A Patient's Story

Living with FAP

A Young Man's Fight Against FAP

- Grandfather, father & paternal aunt were all diagnosed with FAP
- Both his father & aunt have had their colon & duodenum removed
- Father's stomach was also removed due to multiple, advanced precancerous polyps

1997

- Age 9
- Diagnosed with FAP due to rectal bleeding

2000

- Age 12
- Colectomy surgery with ileorectal anastomosis
- Complications required re-operation 3 days later

Annual sigmoidoscopies begin

A Young Man's Fight Against FAP

2009

- Age 21
- Numerous rectal polyps removed; experienced life-threatening hemorrhaging
- Some polyps as large as 2 cm

2010

- Age 22
- A repeat sigmoidoscopy showed the rectum improved with numerous small polyps and one large polyp
- Began upper endoscopy surveillance
- Multiple, small stomach polyps removed; biopsy confirmed fundic gland polyps. In duodenum, multiple small, tubular adenomas were found; biopsy confirmed stage II duodenal polyposis

A Young Man's Fight Against FAP

2010

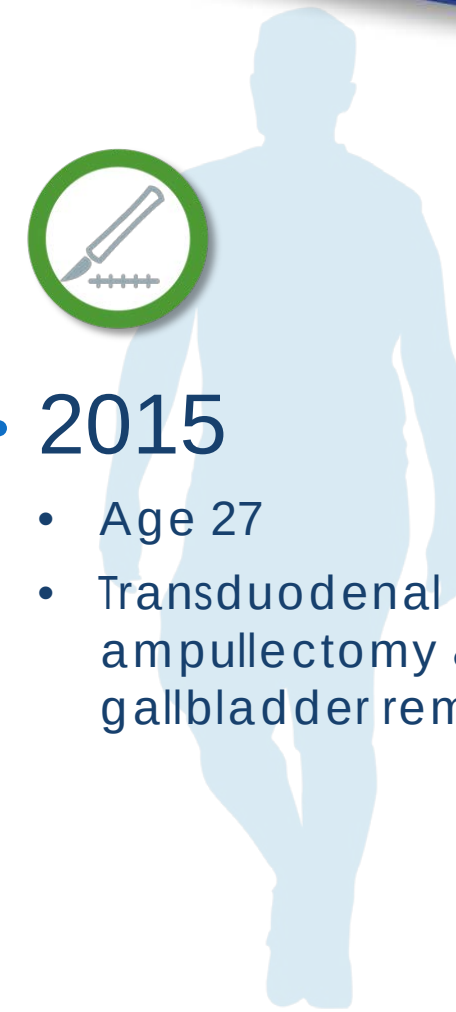
- He continued with esophagogastroduoden-oscopy (EGD) every 3 years
- Because of the risk of passing down the FAP gene, he decided not to have children

2014

- Age 26
- EUS demonstrated precancerous tubulovillous adenoma polyp growing up bile duct & causing intermittent blockage & abnormal liver blood tests

2015

- Age 27
- Transduodenal ampullectomy & gallbladder removal



A Young Man's Fight Against FAP

2016

- He developed pancreatitis, which required hospitalization in the ICU
- Underwent multiple abdominal surgeries for intra-abdominal infections
- Age 28
- He died 8 months later

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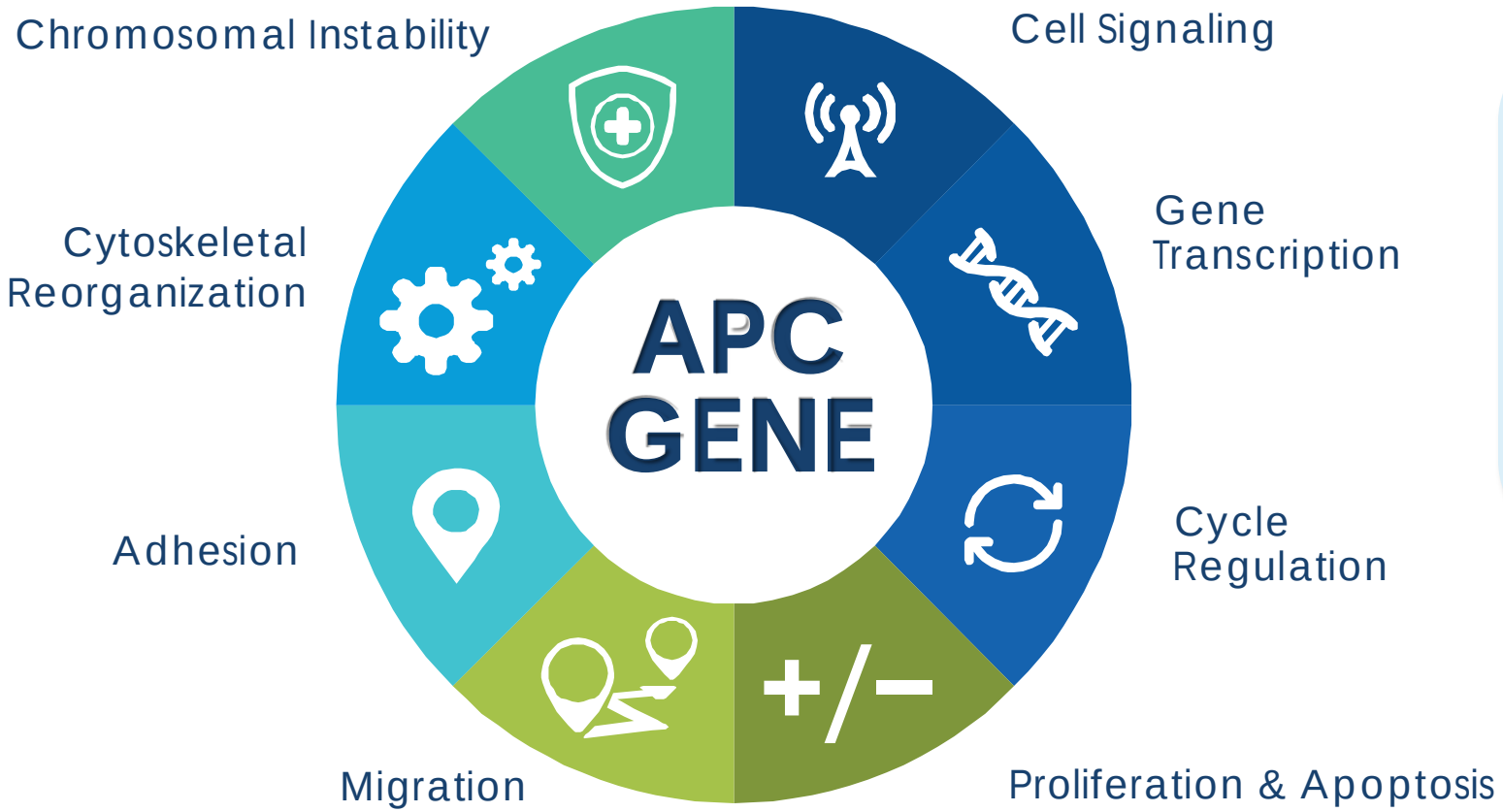
The Science of FAP

The Pathophysiology and Manifestations of FAP

The APC Gene Is Involved in Many Cellular Activities

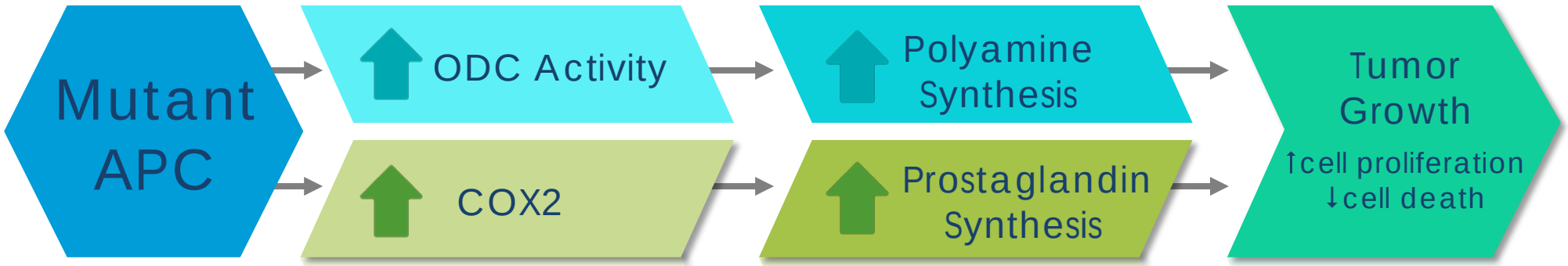


Loss or deregulation of APC may have many consequences, including tumorigenesis

Tumor Suppressor Genes; Volume 1: Pathways and Isolation Strategies; 2003, 520 p.

Pathways to FAP

1. Mutant APC leads to increased ODC & COX2 expression
2. Polyamines (PAs) and prostaglandins are associated with increased proliferation & decreased apoptosis in tumorigenesis
3. ODC is the first enzyme in PA biosynthesis, & COXs are involved in prostaglandin production



Gerner EW, Meyskens, FL; Polyamines and cancer: old molecules, new understanding; Reviews Cancer, 2004; 4: 781–792; Eberhart CE, et al; Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas; Gastroenterology, 1994; 107(4): 1183-8.

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How Is FAP Managed Today?

Surveillance & Interventions in FAP

Current Management of FAP

The current clinical management paradigm for FAP comprises screening, surveillance, & surgery

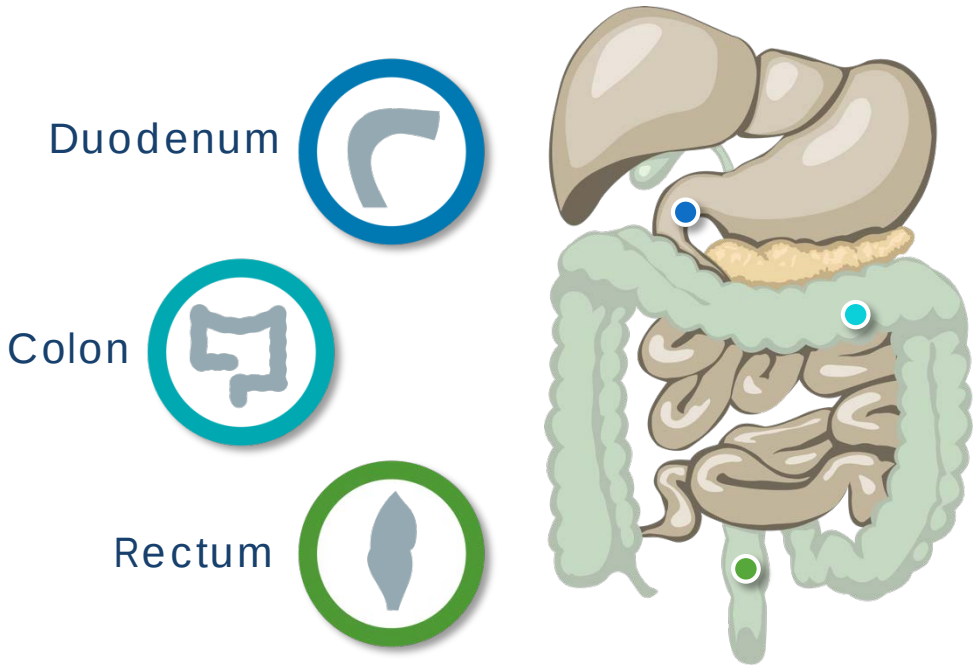
SCREENING	SURVEILLANCE	SURGERY
• Family history	• Pre- or post-surgical	• Colectomy, ileorectal anastomosis (aged 15-25 years)
• Personal history with associated finding • APC mutation test (genetic/panel testing)	• Sigmoidoscopy / colonoscopy • Post-surgical extracolonic surveillance (eg, gastric, thyroid)	• Proctocolectomy, ileostomy or ileal pouch-anal anastomosis • Additional surgeries (based on continued surveillance)
• Polyp count to determine next steps	• Duodenal polyp surveillance (start in the 20s & post-surgical)	

Miller HH, et al. *Int J Psychiatry Med.* 1986;16:211-230; Esplen MJ, et al. *Dis Colon Rectum.* 2004;47:687-695; Andrews L, et al. *Genet Med.* 2006;8:697-703; Douma KFL, et al. *Psycho-Oncology.* 2008;17:737-745.

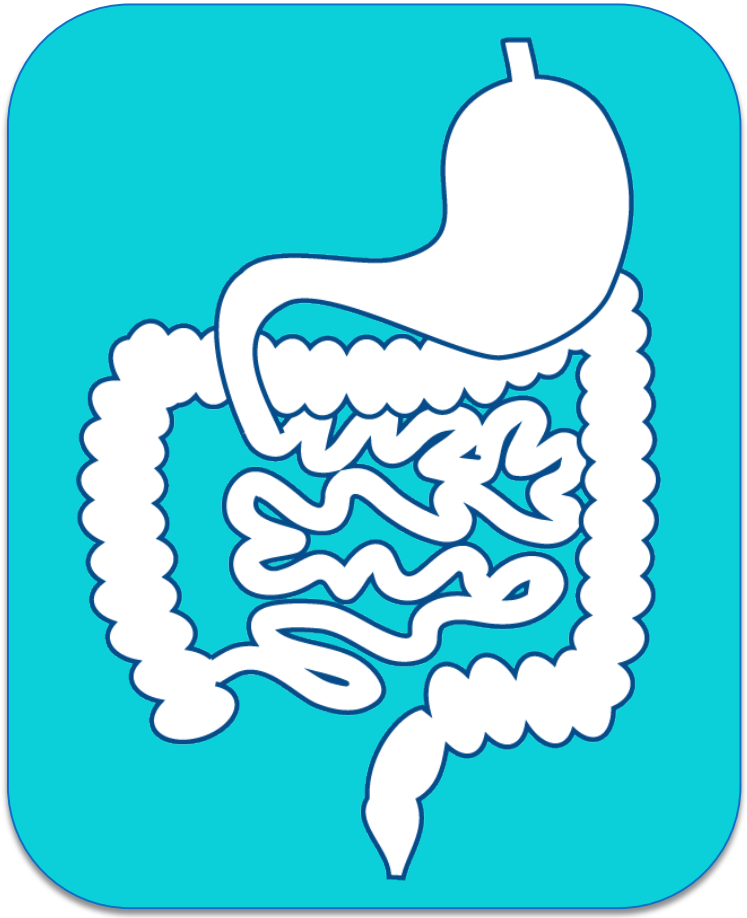
FAP-Related Polyposis Requires Surgery in the Colon & Rectum

- Current interventions are limited to endoscopies and surgeries of the gastrointestinal tract
- Benefit of current interventions are limited, as they only decrease polyp burden & not the underlying disease

Leaving other, extra-colonic manifestations untreated



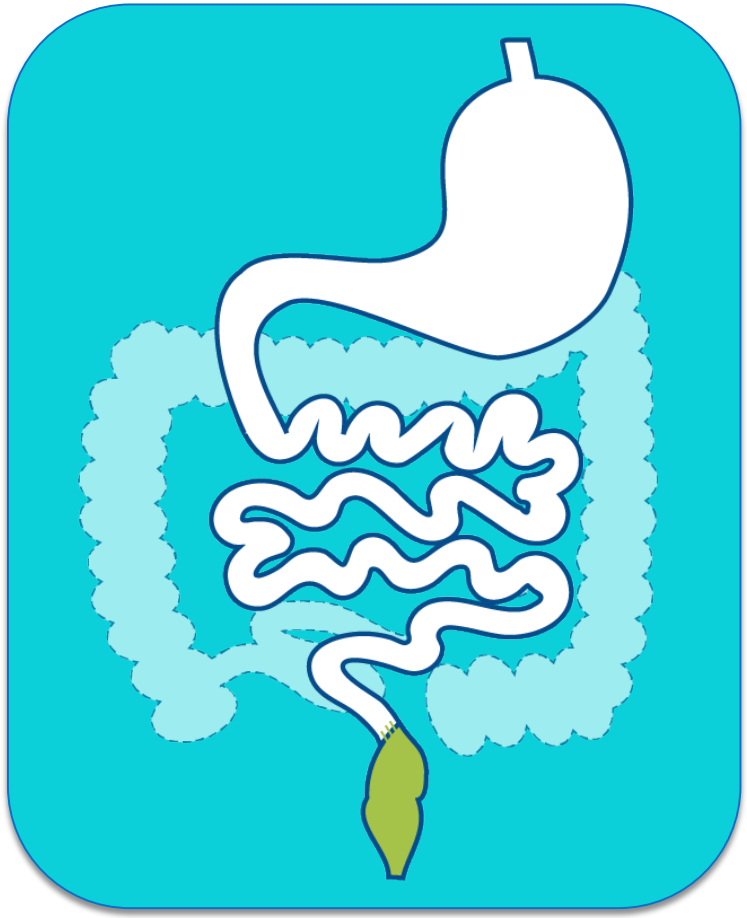
Patients With FAP Undergo a Variety of Surgical Interventions



Patients With FAP Undergo a Variety of Surgical Interventions

Colectomy

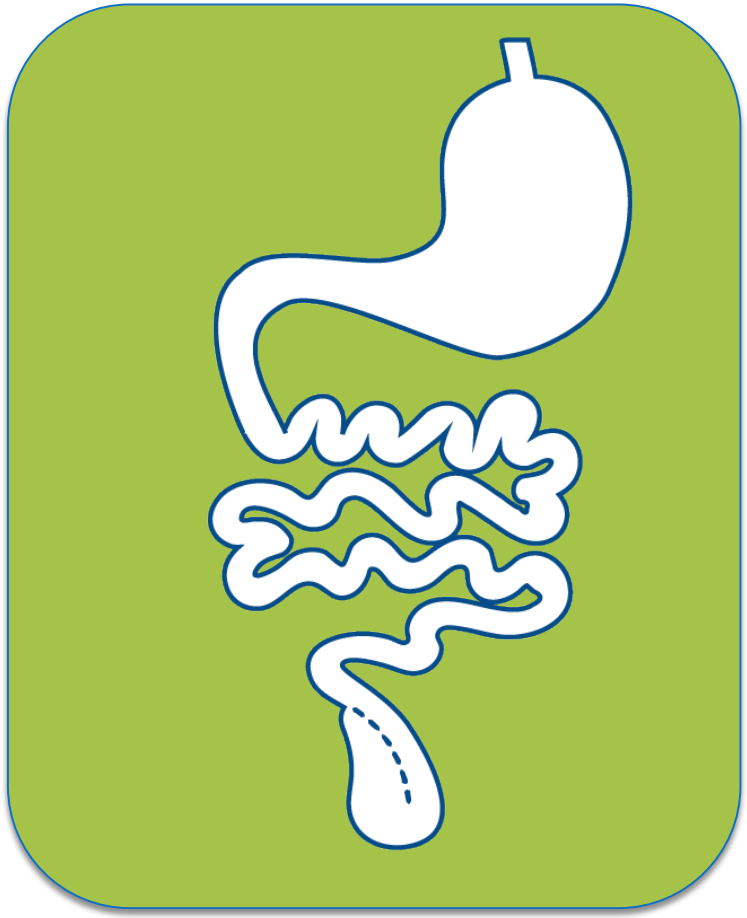
- Complete removal of the colon
- Attach small intestine to rectum
- Desmoid tumors or oligopolyposis



Patients With FAP Undergo a Variety of Surgical Interventions

Proctocolectomy With Ileal Pouch

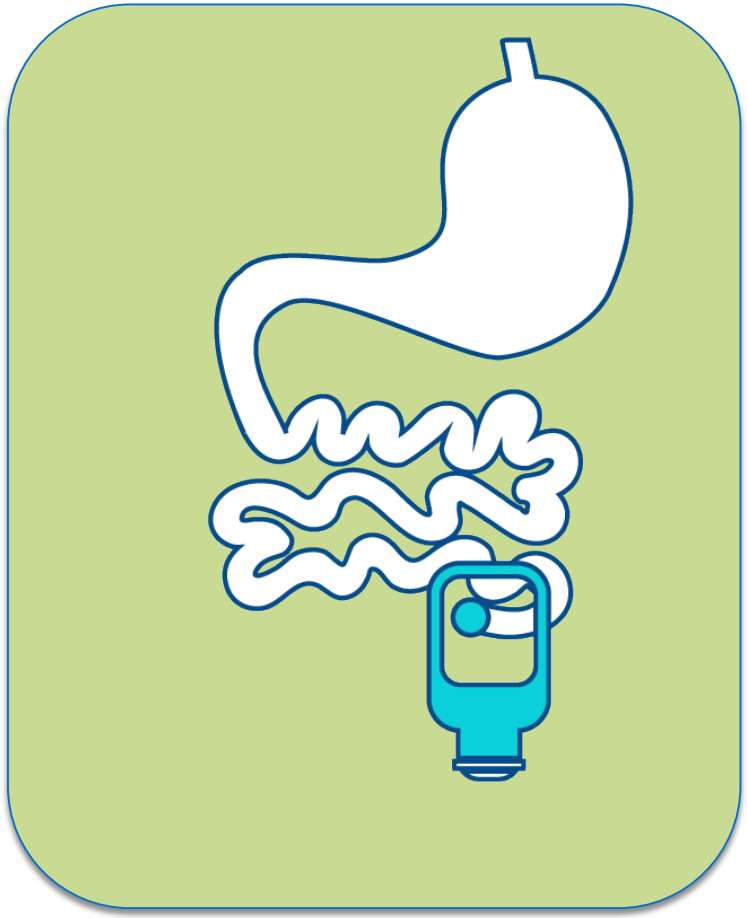
- Removal of the colon/rectum
- Creation of an ileal pouch
- Used when patients have >500 colon polyps, >20 rectal polyps, or CRC



Patients With FAP Undergo a Variety of Surgical Interventions

Colectomy & End Ileostomy

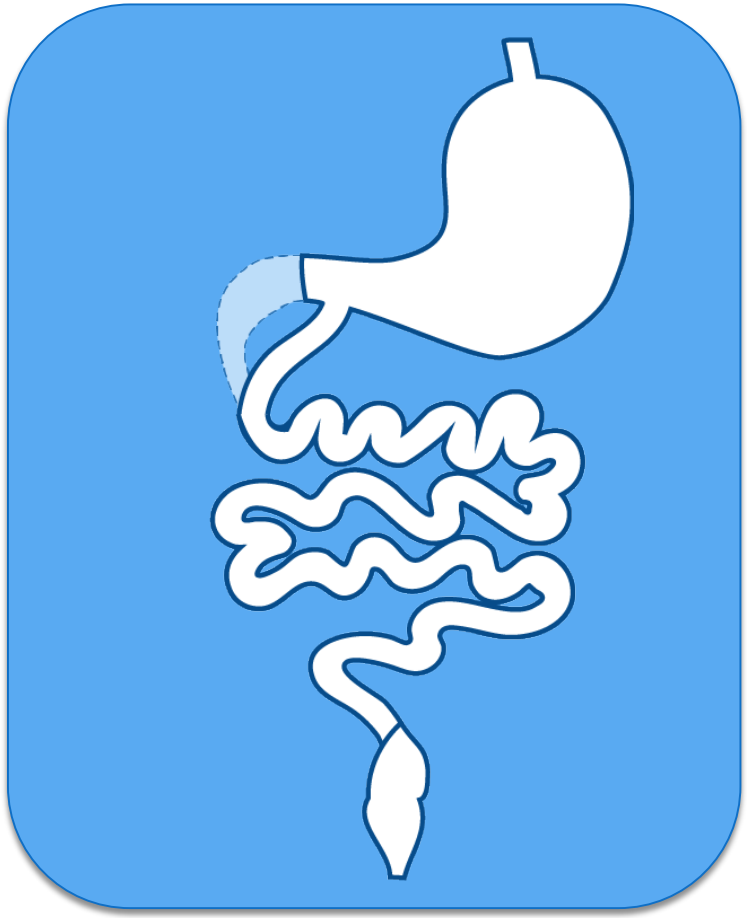
- Rarely used
- Patients have ileostomy bag



Patients With FAP Undergo a Variety of Surgical Interventions

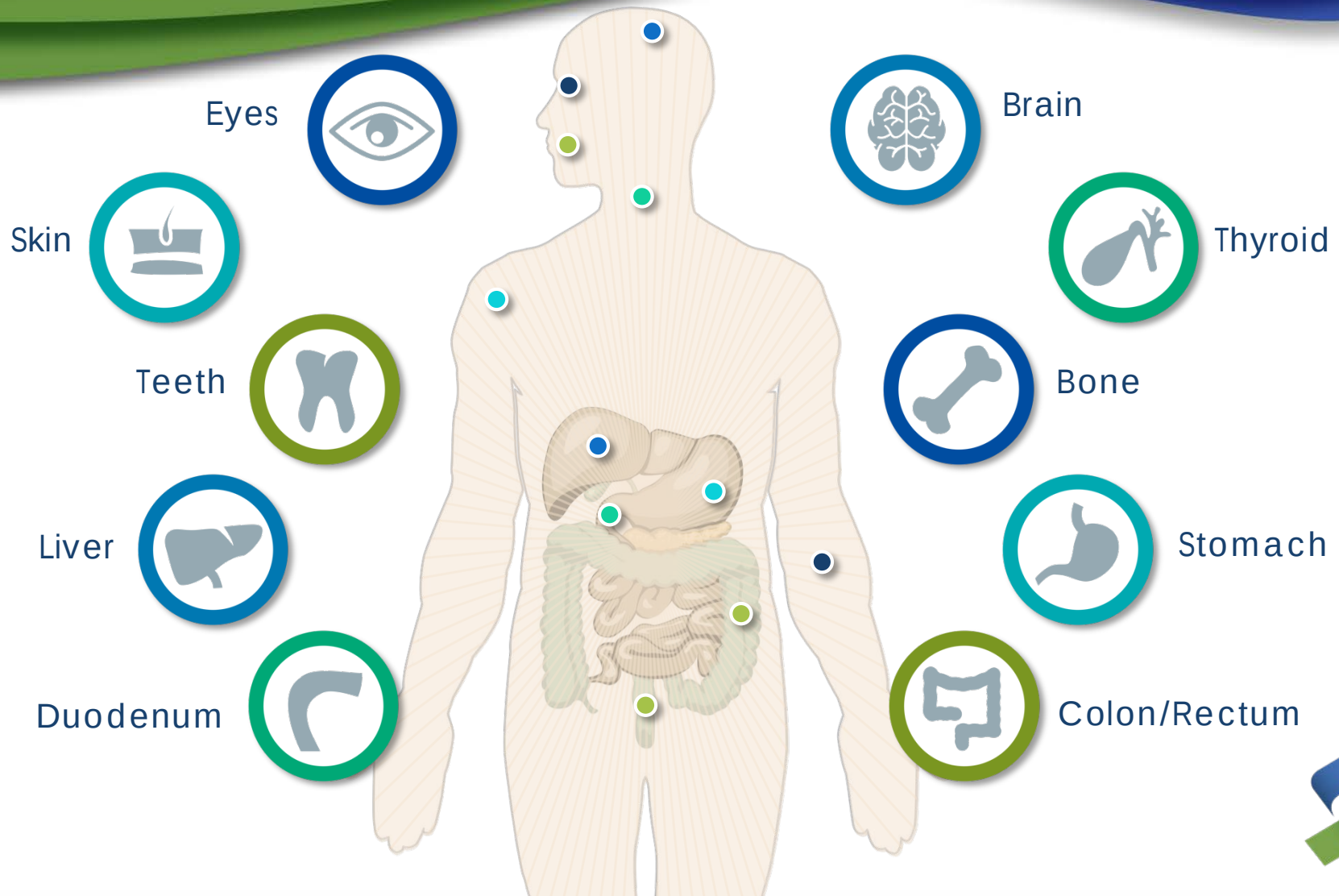
Duodenectomy

- Removal of the duodenum
- For patients with duodenal cancer, advanced duodenal polyposis



Current Interventions Leave Many FAP Manifestations Unaddressed

We need to consider the whole person with FAP



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CPP-1X/Sulindac Program

Addressing the Underlying Mechanism of FAP

CPP-1X/Sulindac Combination of Well-Characterized Molecules

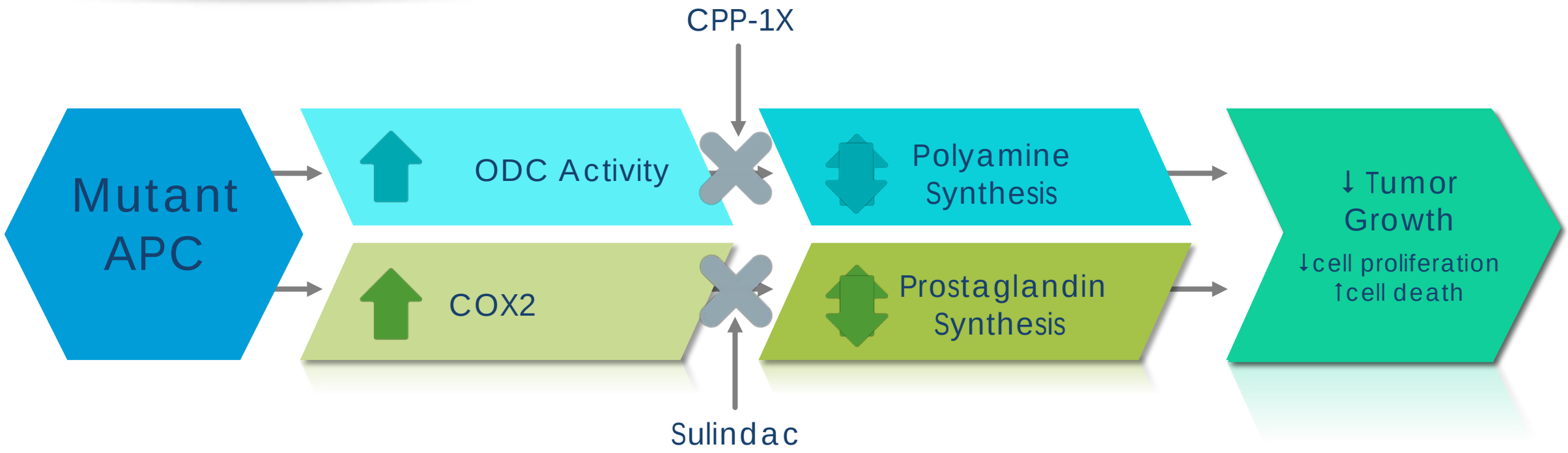
Eflornithine (DFMO) also known as CPP-1X

- Enzyme-activated, irreversible ODC inhibitor
- No approved oral form
  - IV formulations used for African Sleeping Sickness
  - Topical formulation (no systemic effect) used for hirsutism (excessive hair growth)

Sulindac

- Inhibits COX2 enzyme
- NSAID with multiple indications

CPP-1X/Sulindac Reduces Polyps in 2 Ways



Strong Data Predict Success of Current FAP-310 Pivotal Trial

Preclinical studies:
APC Min mouse polyposis & colon cancer model, showing compelling regression & prevention effect of CPP-1X, NSAID, & combo

Clinical regression:
Familial polyposis. Phase 2 FAP trial with CPP-1X/NSAID combo

Clinical prevention:
Sporadic polyposis. Phase 2/3 Meyskens trial CPP-1X/sulindac combo, showed highly significant prevention effect

Giardiello FM, et al. *Cancer Res.* 1997;57:199-201; Ignatenko NA, et al. *Nutr Cancer.* 2008, 60 Suppl 1:30-35; Lynch PM, et al. *Gut.* 2016;65:286-295; Meyskens FL, et al. *Cancer Prev Res.* 2008;1:32-38

FAP Phase 2 Trial Proof-of-Concept Study

112 PATIENTS
(evaluable data for 68)

Randomized equally to 1 of 2 treatment groups

6 months of daily treatment

Positive trends in all endpoints

Global video assessment:

- Showed statistically significant regression in secondary endpoint*
- Is likely a stronger indicator of potential clinical benefit than counting polyps in a designated area

CPP-1X (750 mg)

+

NSAID
(400 mg celecoxib B.I.D.)

NSAID
(400 mg celecoxib B.I.D.)

ENDPOINTS

Primary: counting polyps in designated areas of the bowel

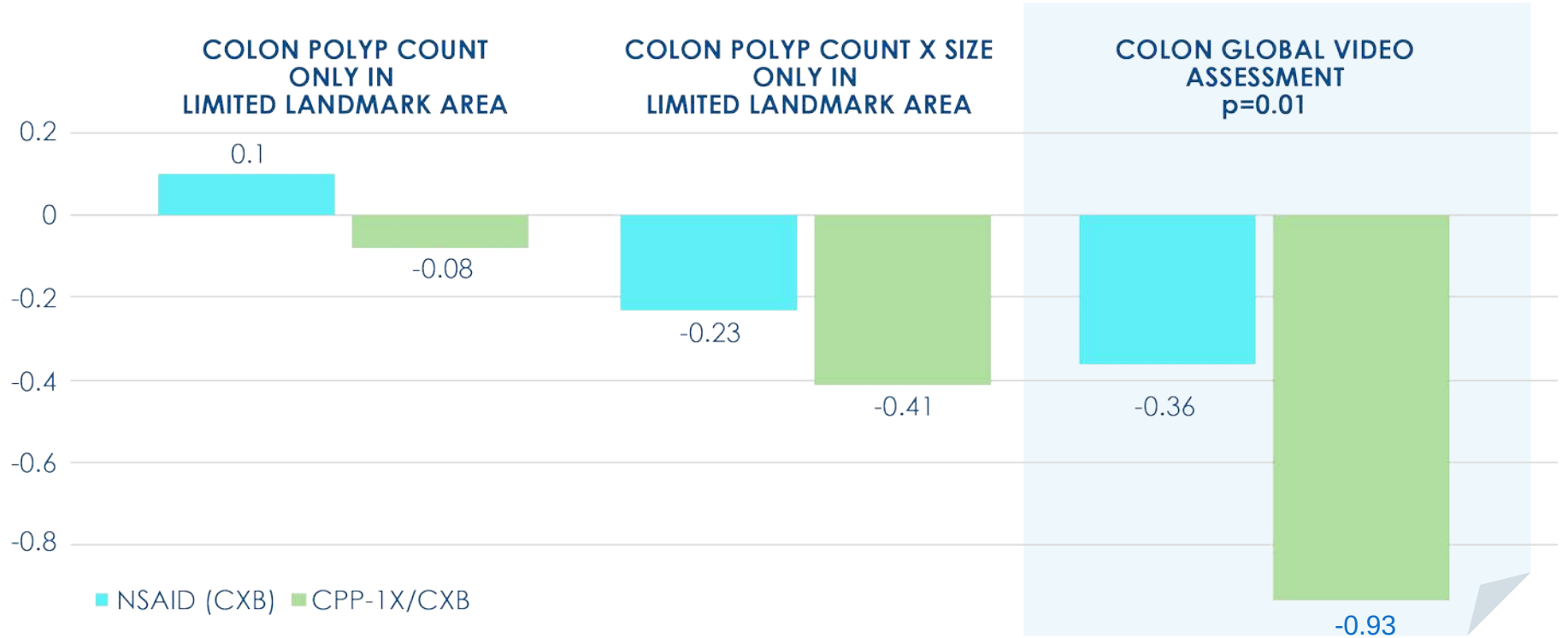
Secondary (A): changes in polyp burden (# & size) via still image assessment in small defined area of bowel

***Secondary (B): changes in global polyp burden (# & size) by multiple expert reviews of video from 4 segments of colon & rectum**

Lynch PM, et al. *Gut.* 2016;65:286-295.

FAP Phase 2 Proof-of-Concept Study Results

Results for all evaluable patients



Lynch PM, et al. *Gut.* 2016;65:286-295.

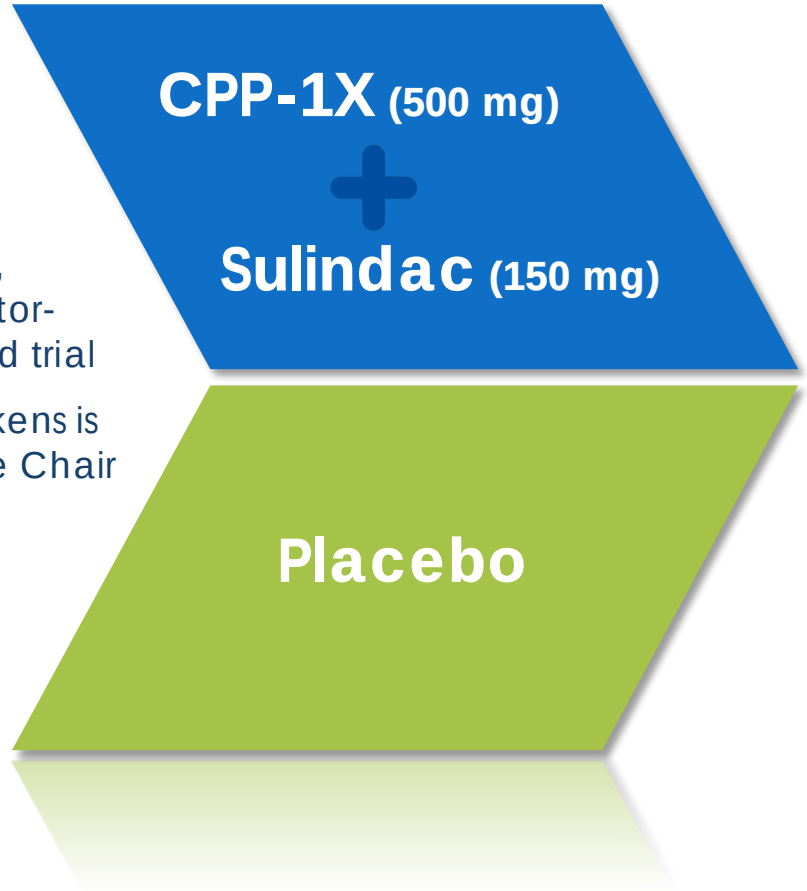
Phase 2/3 Meyskens Trial in High-risk Polyp Formers

375 PATIENTS
(At high risk for polyp formation & recurrence)

Prospective, randomized, placebo-controlled trial
(1:1 randomization)

3 years of daily treatment

- UC Irvine, investigator-sponsored trial
- Dr. Meyskens is Associate Chair of SWOG



ENDPOINTS

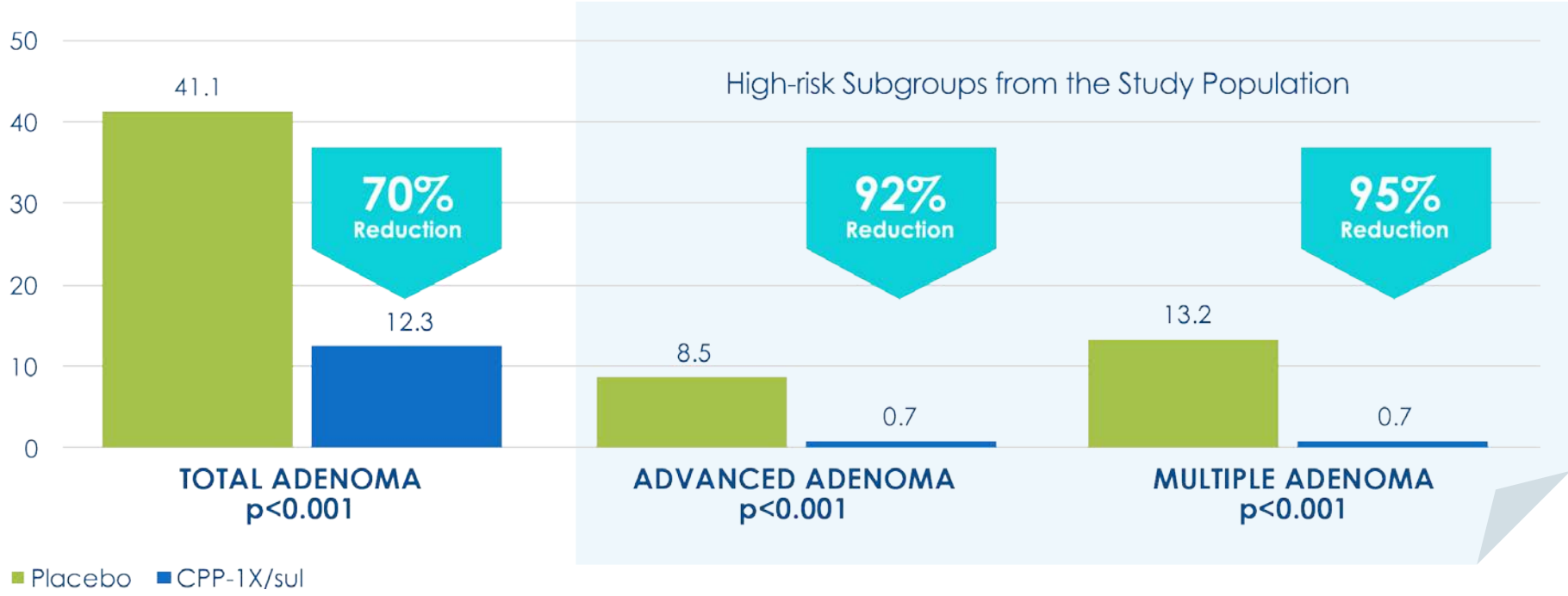
Primary: polyp occurrence

Meyskens FL, et al. *Cancer Prev Res.* 2008;1:32-38.

Phase 2/3 Meyskens Trial Efficacy Results

Marked reduction of polyps (adenomas) with CPP-1X/sulindac daily treatment

Percentage of patients with metachronous adenomatous polyps (at 3 years)



Meyskens FL, et al. *Cancer Prev Res.* 2008;1:32-38.

CPP-1X/Sulindac Combination Has Extensive Clinical Activity & Minimal Toxicities

- CPP-1X (eflornithine) used in many previous NCI-funded trials
- Ototoxicity (hearing loss) only for specific genetic subgroup, which may be a useful genetic screening tool to predict those most likely to respond to the drug & to have minimal side effects
- Molecular diagnostic & clinical criteria strategies to manage low-frequency toxicities in the future
- Sulindac approved for arthritis & used extensively for many years
- No statistical significant difference in serious adverse events in Meyskens trial between placebo and CPP-1X/sulindac with 375 patients and 3 years of daily dosing

Zell JA, et al. *J Natl Cancer Inst.* 2010;102:1513-1516.

The ABCs of FAP: Essential Points to Remember

A

FAP is a rare, life-threatening disease characterized by the development of 100s to 1000s of colorectal adenomas

1/10,000
US prevalence

▶ ***Today, clinicians focus on the colon and rectum***

B

Left untreated, the lifetime risk for CRC is ~100% by age 40-50 years, if colectomy not performed

~100%
lifetime risk of CRC

▶ ***Today, prophylactic colectomy is recommended in early adulthood***

C

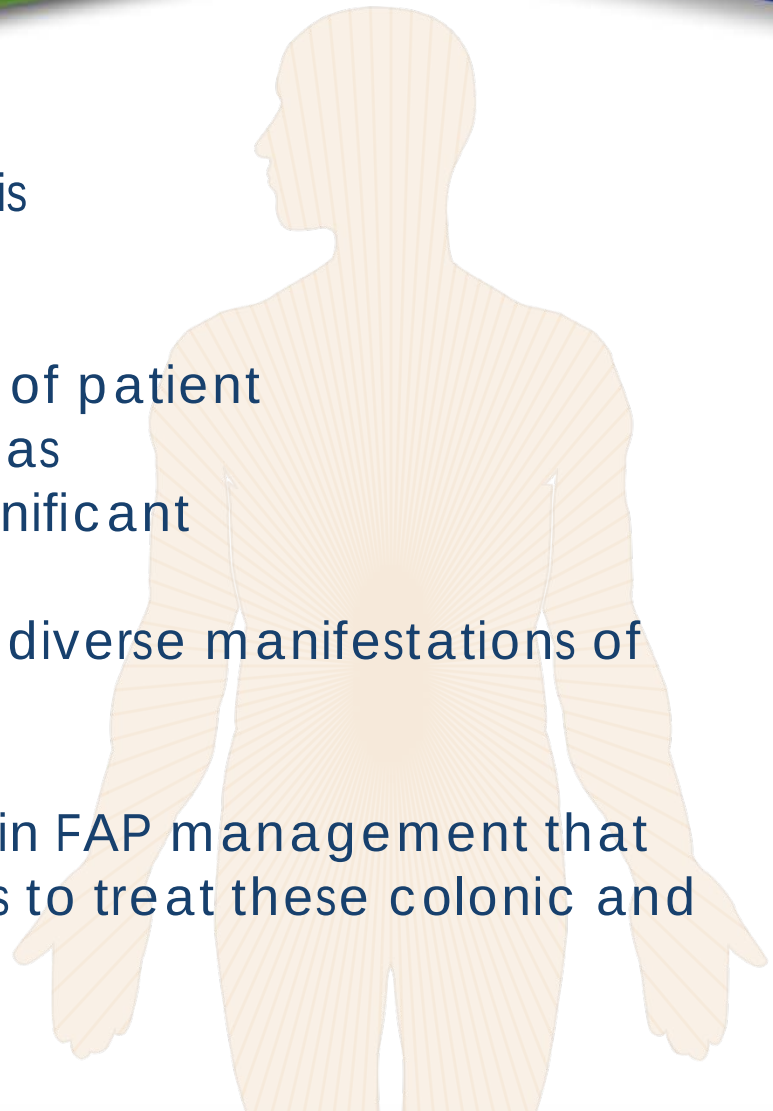
Extracolonic manifestations: 5 or more organs & systems affected by FAP

5 organs
& systems affected

▶ ***However, colectomy does not address these other disease manifestations***

Consider the Whole Person With FAP

- FAP is a chronic progressive disease that is life-threatening if left untreated
- The burden associated with FAP, in terms of patient medical and psychosocial needs as well as multisystem evaluation & treatment, is significant
- Surgical interventions do not address the diverse manifestations of the disease
- There is an unmet need for future efforts in FAP management that address the underlying mechanisms so as to treat these colonic and extra-colonic manifestations of disease



Phase 3 Pivotal Trial

Peter Kiener, D. Phil

Chief Scientific Officer

Sucampo Pharmaceuticals, Inc.

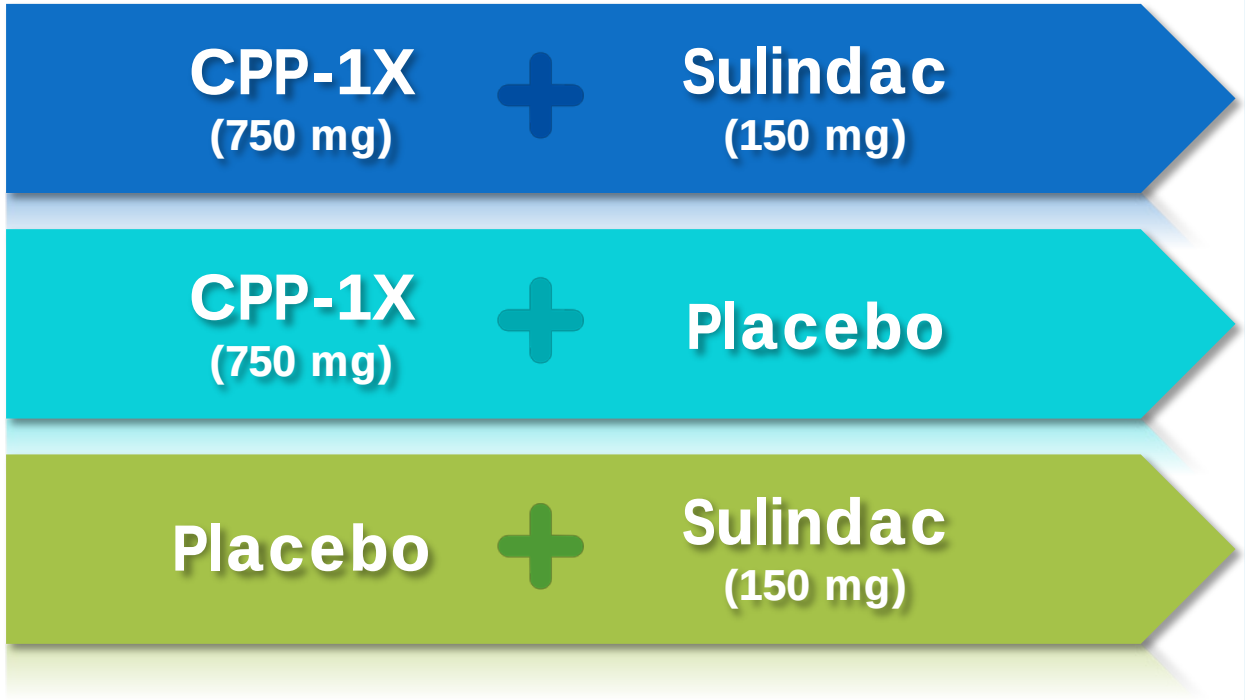
FAP-310 Phase 3 Pivotal Trial Design

171 PATIENTS
Randomized equally to 1 of 3 treatment groups

(1:1:1 randomization)

Two years of daily treatment

Subjects were enrolled in 11 sites in the US and Canada & 6 in Europe



ENDPOINT

'Time to FAP-related event'

Over 24 months at any disease site per patient with up to 2-year extension

Inclusion Criteria:

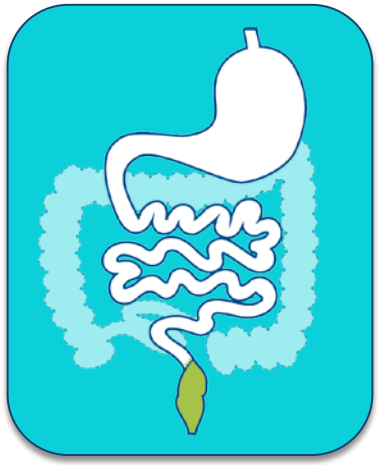
- 18 years of age or older
- Diagnosis of phenotypic classical FAP with disease involvement of the duodenum and/or colon/rectum/pouch.
  - Genotype: APC mutation required
  - Classical FAP Phenotype: >50 adenomatous polyps
- UGI endoscopy/LGI endoscopy (proctoscopy/colonoscopy) performed within 30 days of randomization.

Definition of “Events” in FAP-310 Trial

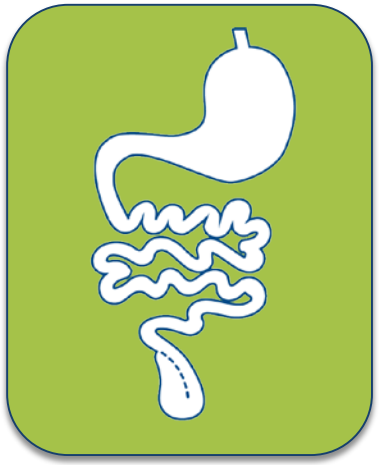
The trial is focused on “FAP-related events” in the GI tract, these include:

- FAP-related excisional intervention (snare polypectomy or surgery) involving the colon, rectum, pouch, duodenum and/or
- Clinically important events which includes progression to more advanced duodenal polyposis (Stage 2, 3, or 4), cancer, or death

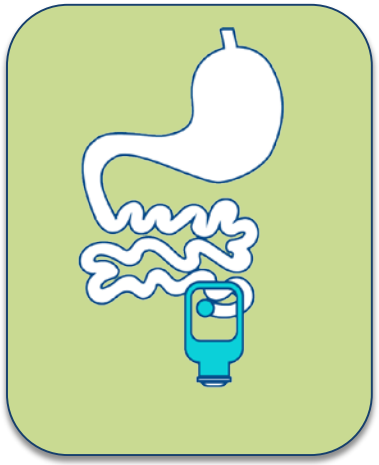
Snare Polypectomy



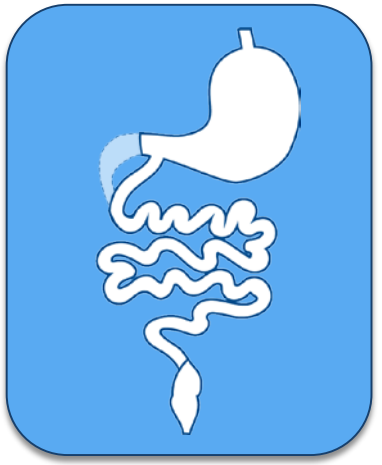
Colectomy



Proctocolectomy
With Ileal Pouch



Colectomy &
End Ileostomy



Duodenectomy

FAP-310 Update

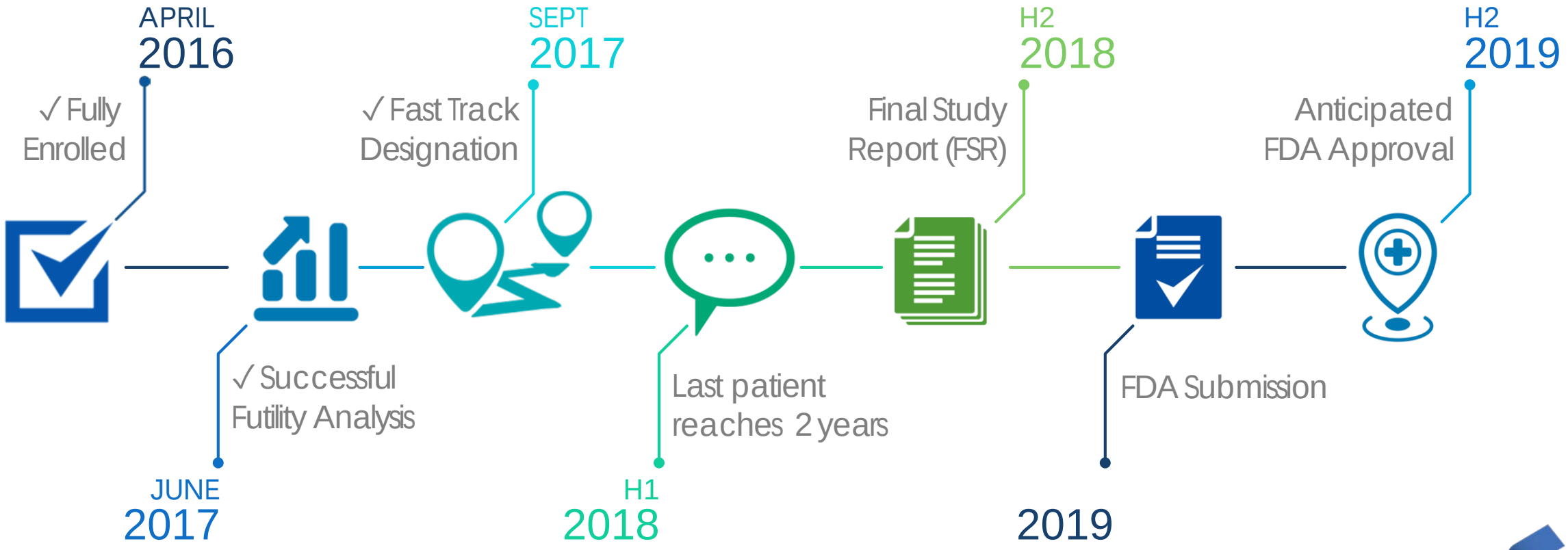
An extension allows for up to 48 months of treatment for subjects that have not had an FAP-related event

Patient treatment will continue until one of the following occurs:

- Subject has FAP-related event or comes off study for other reasons
- 90 FAP-related events have occurred
- At the decision of the sponsor*, last patient in (LPI) has reached
  - Minimum 24 months of treatment or
  - Minimum of 30 months of treatment or
  - Minimum of 36 months of treatment

* with recommendation of DMC

Milestones to Approval



Applying for PRIME in EU which is analogous to Fast Track – targeted submission 4Q 2017

The Promise of Combination Therapy With CPP-1X/Sulindac

- In clinical trials conducted to date, combination therapy with low doses of CPP-1X/sulindac produced marked inhibition of colorectal adenomas & exceeded the effects of single agents

- Moreover, combination CPP-1X/sulindac has not been associated with any significant toxicity in these clinical studies

- Novel "combination pharmacoprevention" is a promising approach to maximize therapeutic efficacy & diminish toxicity in patients with FAP
- Disruptions of these pathways is likely relevant in other tumors such as colorectal adenomas and pancreatic adenocarcinoma

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Questions & Answers

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Break

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Niemann-Pick Type C (NPC)

Paul Gissen, MBCHB, PhD

Professor of Metabolic Diseases

University College of London

Consultant in Paediatric Metabolic Diseases

Great Ormond Street Hospital for Children, London, UK

Our Discussion Today - Niemann-Pick Type C (NPC)

- Intro to NPC
- Current Management Options
- VTS-270 Phase 2/3 Trial
- Real Impact of NPC
- VTS-270 Program

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Introduction to NPC

Presentation, Clinical Features, Challenges in Diagnosis, & Future Diagnostic Approaches

NPC is a Rare, Progressive, Neurodegenerative, & Ultimately Fatal Disease that can Present at Any Age

- NPC occurs with an incidence of 10.4–11.2/million/year live births[1,2]
  - Considered an under-estimate of the true prevalence
  - Atypical phenotypes may not be clinically suspected
  - High premature mortality rate following neurological onset
- NPC may be misdiagnosed or never detected[3]
- Prevalence reports of estimated 2000–3000 cases globally[1,2]
- Intracellular lipid trafficking dysfunction in the spleen, liver, lungs, bone marrow, & brain[4]
- NPC[1] gene is responsible for ~95% cases of NPC disease[4]

1. Vanier MC, et al. *Orphanet J Rare Dis.* 2010;5(16):1-18. 2. Wassif CA, et al. *Genet Med*. 2016;18:41-48 3. Burlina A. *J Neurol.* 2014;261:S525-S527. 4. Vanier MT. Niemann-Pick Diseases. In: Dulac O, Lassonde M, Sarnat HB, eds. *Handbook of Clinical Neurology.* 3rd ed. Elsevier B.V; 2013:1717-21.

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What Is the Real Impact of NPC?

Meet Patient NC

Baby Girl

- Birth - age 4
- Normal birth & delivery
- No difference from any baby or young child

Age 5

- Initial presentation
- NPC not recognized
- Diagnosed with speech & language delay

Age 10

- NPC not recognized
- Referred to pediatric neurologist
- Menarche

- Progressive gross and fine motor control difficulty
- Vacant episodes + 1X episode of GTC epilepsy

Meet Patient NC

Age 11

- Social impact: mood swings, “vile temper”
- End of mainstream school
- Speech very unclear
- Abnormal eye movements

Normal exams:

- Brain MRI
- VER & ERG
- Physical exam
- Repeat EEG

Age 13

- 1st misdiagnosis
- Epilepsy
  - Difficult to control
  - Multiple seizure types
- Obesity
- Diagnosed with ***LENNOX-GASTAUT SYNDROME***

Meet Patient NC

Age 14

- 2nd misdiagnosis considered
- Worsening epilepsy
- MRI: generalized atrophy with no focal defects
- Worsening ataxia
- Worsening dysphagia

Normal exams:

- Investigation for ***BATTEN'S DISEASE***
- Chitotriosidase & hexaosaminidase, EEG & CT of head, Metabolic screen, TFTs, LFTs, FBC, VLCFAs, urea & electrolytes, ammonia, lactate, CrK, virology

Age 15

- 3rd misdiagnosis considered
- Neuroregression
- Progressing dysphagia
- Nasogastric feeding tube
- Head nodding
- Investigated for ***RETT'S SYNDROME***

Meet Patient NC

Diagnosed 11 Years After Initial Presentation

Age 16

- **Referred to additional pediatric center**
- Recurrent digital fracture
- Profound seizures
- Gaze palsy
- Cataplexy
- Significant dysphagia with aspiration
- Weight loss

- **NPC suggested as differential diagnosis**
- Diagnosis made by filipin staining
- Disease too advanced for disease-specific treatment

Age 18

- Died due to aspiration pneumonia

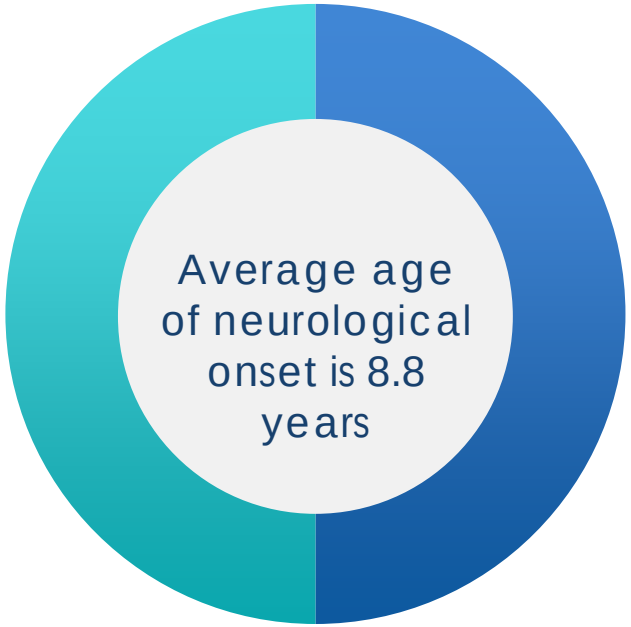
Variable Clinical Presentation Causes Diagnostic Challenge for Physicians

- Variable age of onset and clinical features
- Visceral presentation mainly limited to neonatal
  - Unexplained neonatal jaundice, [hepato]splenomegaly
  - Resolves when survived
- Neurological presentation
  - Psychiatric presentation with older patients
    - Cognitive decline or dementia, psychotic symptoms
- Biochemical diagnosis is not clear-cut, but screening tests make it easier

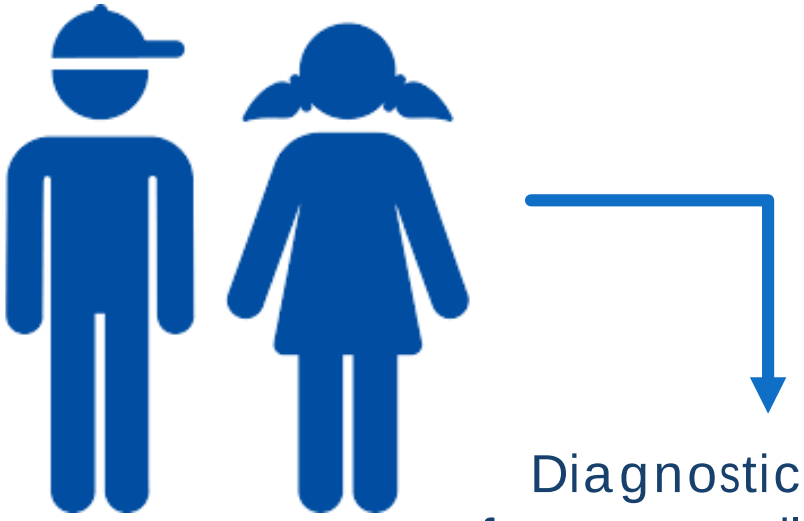
VSGP, vertical supranuclear gaze palsy

Average Age at Diagnosis is 10 Years

NPC Disease UK Database: Delayed Diagnosis



Average age at diagnosis is 10.4 years



Diagnostic delay – often not until advanced disease progression

Imrie J, et al. *BMC Neurology.* 2015;15:257.

Broad Impact of Neurological & Psychiatric Features

- Time to diagnosis limited by symptomology exhibited and level of disease awareness of healthcare professionals[1]
- Neurological involvement defines the disease severity in most patients
  - Typically preceded by systemic signs[2,3]

NEUROLOGICAL

- Gelastic cataplexy
- High-frequency hearing loss
- Developmental delay
- Progressive cerebellar ataxia & cognitive impairment
- Delayed motor development w/ loss of gross & fine motor function
- Difficulty in school
- Seizures
- Dysphagia
- Dysarthria
- Clumsiness
- VSGP*

PSYCHIATRIC

- Early-onset psychosis
- Schizophrenia
- Depressive syndrome

*VSGP, vertical supranuclear gaze palsy

1. Klunemann H, et al. *Eur Neuro Rev.* 2011;12-15. 2. Patterson MC, et al. *Orphanet J Rare Dis.* 2013,8:12. 3. Vanier MT. *Orphanet J Rare Dis.* 2010;5:16.

Disease Progression is Irreversible After the Onset of Neurological Symptoms

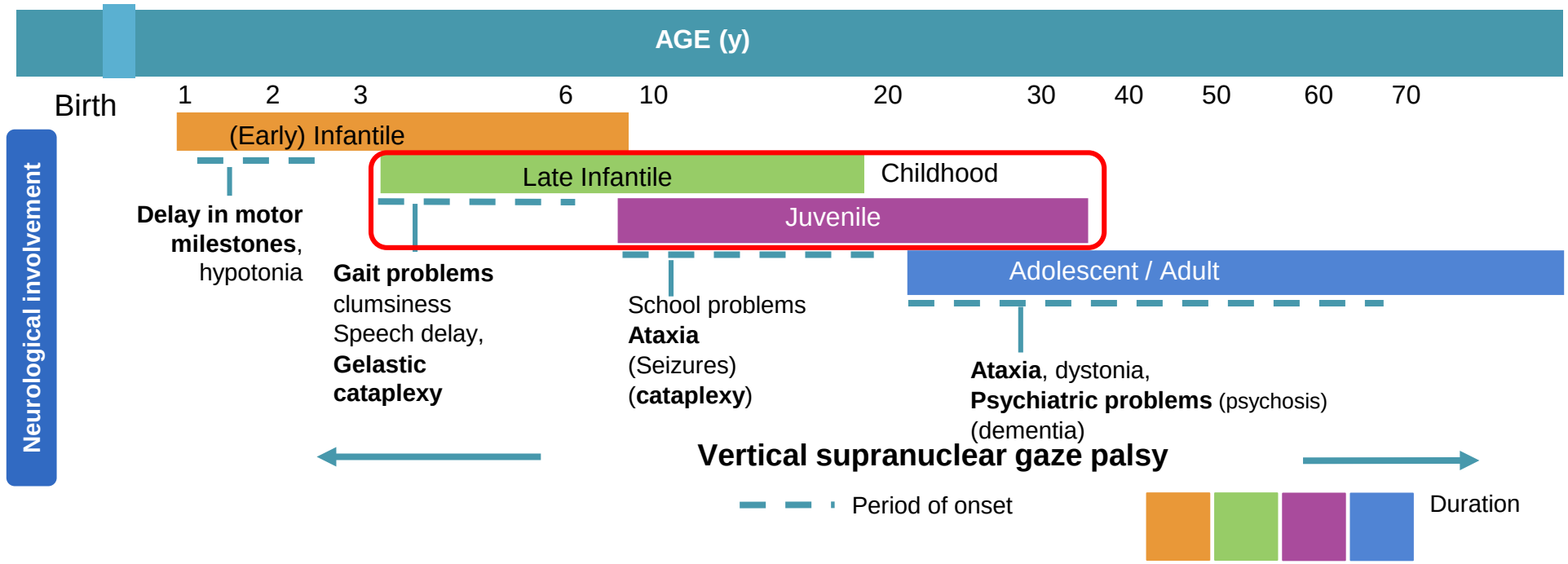
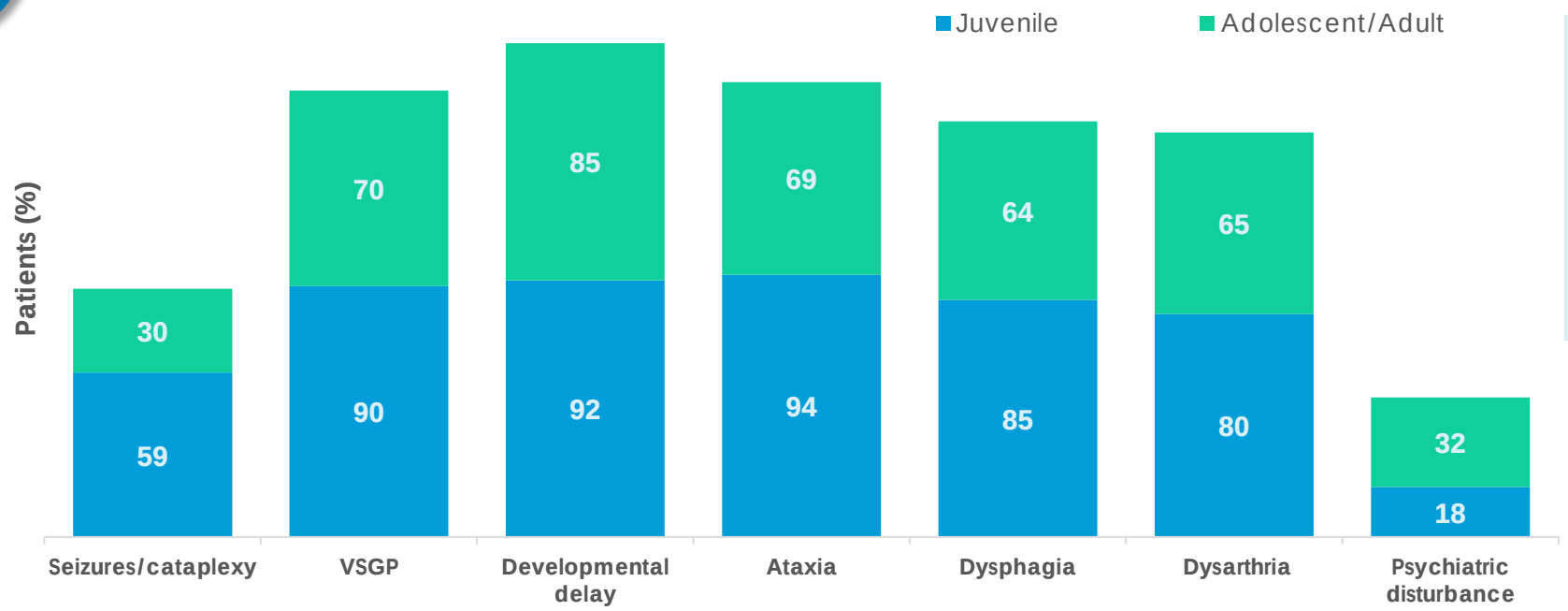


Figure reproduced from Vanier MT. *J Inherit Metab Dis.* (2015)38:187.

Neurodegenerative Presentation Major Driver of Morbidity Regardless of Age of Onset

Lipid accumulation in CNS results in progressive & irreversible neuronal degradation



UK Observational Cohort (N=146 patients born between 1954 & 2009)

The mean (SD; range) age at neurological onset in this subgroup was 4.1 (1.2; 0.4–8.0) years

VSGP, vertical supranuclear gaze palsy
Imrie J et al. *BMC Neurol.* 2015;15:257.

Neurodegenerative Presentation & Sequalae are Major Causes of Mortality

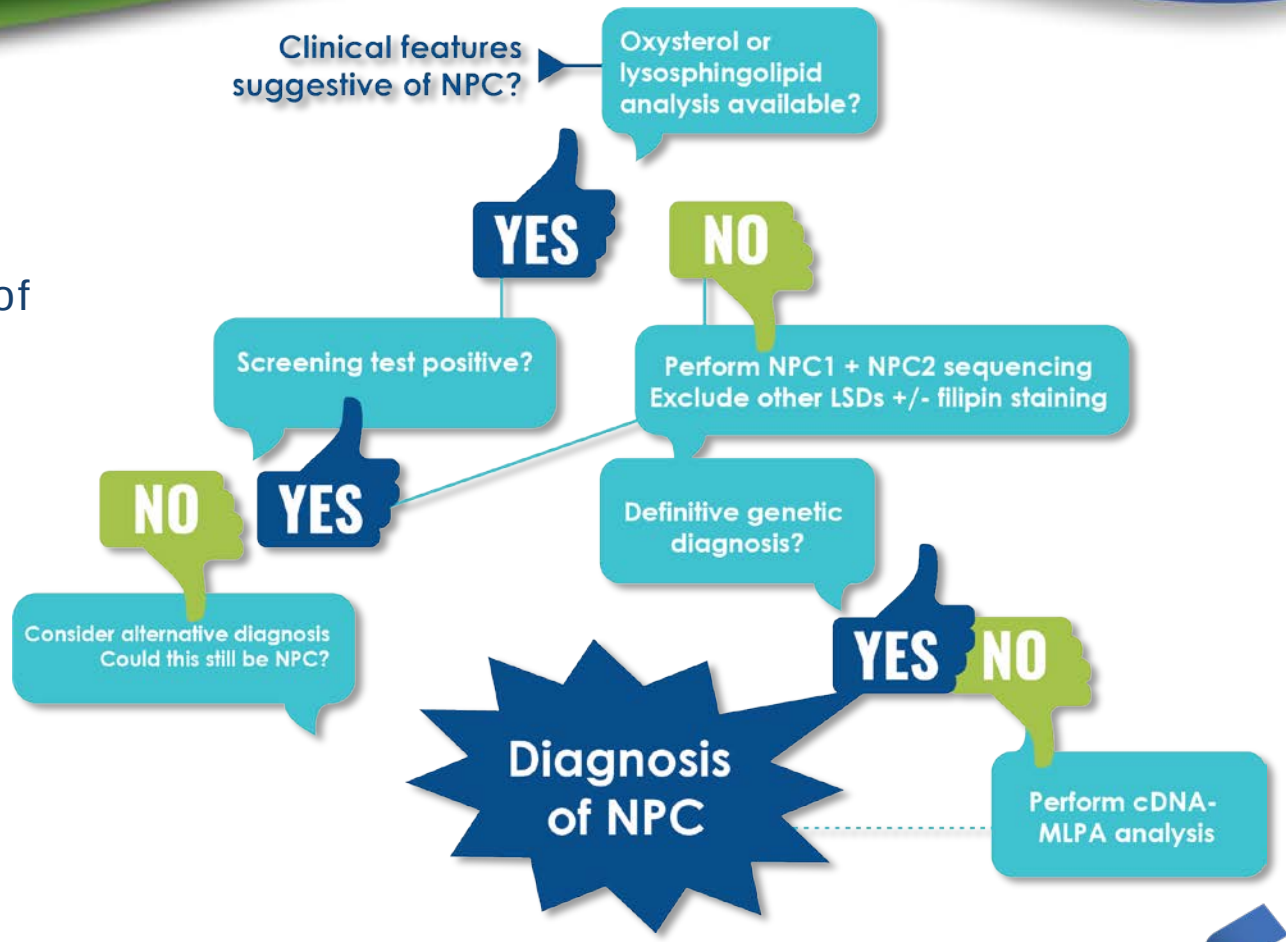
- Mortality usually results from the neurological manifestations
  - Dysphagia leads to consequent aspiration pneumonia[1-3]
    - Aspiration pneumonia-related mortality was reported in >20% of patients, but this is likely to be an underestimate[1]
  - Bronchopneumonia accounts for death in >60% of patients[1]
  - Exacerbated by the delays in diagnosis[1-3]

Patient NC Died at age 18 due to aspiration pneumonia

1. Walterfang M, et al. *Orphanet J Rare Dis.* 2012;7:76. 2. Jan MM, et al. *J Child Neurol.* 1998;13:75-78. 3. Kelly DA, et al. *J Pediatr.* 1993;123:242-247.

Evolving Diagnostics will Lead to Earlier Diagnosis

- Filipin staining of unesterified cholesterol in cultured skin fibroblasts
  - Gold standard, but variant phenotype in 15% of cases[1,2] (higher proportion in adult cases); not 100% specific for NPC
- Sequencing of NPC1 and NPC2
  - >450 mutations known, some deep intronic
- New biomarkers
  - Plasma oxysterol analysis,[3,4] using GC/MS or LC-MS/MS
    - Some overlap with heterozygous carriers
  - Bile acids[5] and plasma lysosphingomyelin[6]



cDNA-MLPA, multiplex ligation-dependent probe amplification of complementary DNA; GC, gas chromatography; LC, liquid chromatography; LSDs, lysosomal storage disorders; MS/MS, tandem mass spectrometry

1. Wraith JE, *et al. Mol Genet Metab.* 2009;98:152–165; 2. Vanier MT and Latour P. *Methods Cell Biol.* 2015;126:357–375; 3. Porter FD, *et al. Sci Trans Med.* 2010;2:56ra81; 4. Jiang X, *et al. J Lipid Res.* 2011;52:1435–1445; 5. Maekawa M, *et al. Steroids.* 2013;78:967–972; 6. Welford RWD, *et al. PLoS ONE.* 2014;9:e114669.

NPC Summary

- NPC is a rare, progressive, neurodegenerative and fatal disease that can present at any age
- A wide range of non-specific manifestations of NPC often lead to delays in diagnosis and misdiagnosis
- A multi-disciplinary approach necessary
- New cheaper, reliable, and sensitive biomarkers for NPC are now available
- Earlier diagnosis can lead to better outcomes with therapies in development

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Current Management Options for NPC

Dan Ory, MD

Professor of Internal Medicine, Cell Biology and Physiology

Washington University School of Medicine, St Louis, MO

There Is Currently No Cure for NPC

Symptomatic & palliative therapies

- Supportive therapies variably effective, alleviate numerous clinical problems associated with NPC[1]
- Seizure
  - Antiepileptics
- Cataplexy
  - Tricyclic antidepressants
  - CNS stimulants
- Dystonia and tremor
  - Anticholinergics
  - Trihexyphenydil
  - GABA derivatives
- Psychosis
  - Atypical antipsychotics

NPC – specific therapies

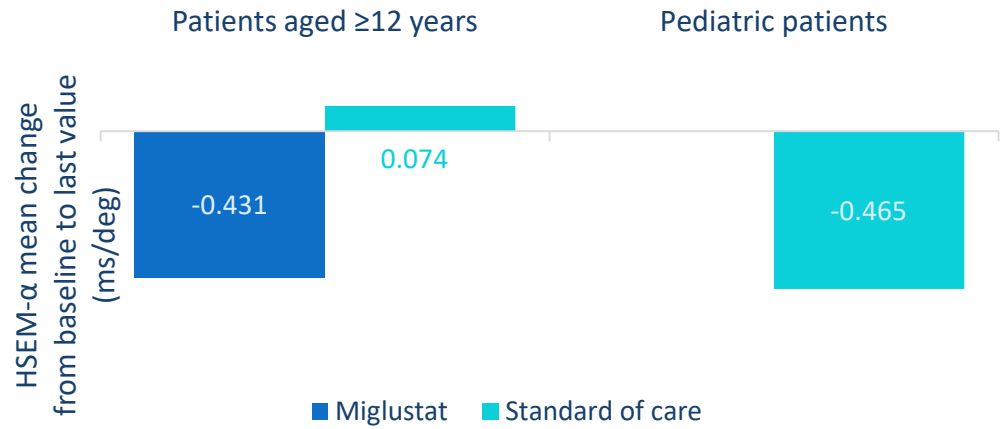
- Miglustat
  - MOA: Oral glucosylceramide synthase inhibitor
  - Utilizes indirect mechanism of action for NPC to limit lysosomal lipid accumulation

1. Patterson MC, et al. *Mol Genet Metab.* 2012;106(3):330-344. 2. Wraith & Imrie. *Understanding Niemann-Pick disease type C and its potential treatment.* 2007. Blackwell Publishing, Oxford UK. 3. Vanier MC, et al. *Orphanet J Rare Dis.* 2010;5(16):1-18.

There are Currently No Treatments for NPC that Directly Address the Pathophysiology of Disease

- In Europe, miglustat indicated for the treatment of progressive neurological manifestations in adult and paediatric patients with Niemann-Pick type C disease[1]
- Miglustat is not approved for Tx of NPC in the US

Miglustat failed to achieve its primary endpoint in patients with NPC[3]



- The primary end point of horizontal saccadic eye movement velocity at 12 months was non-significantly improved with miglustat therapy vs standard care (*P*=0.091)

1. Zavesca (miglustat) Summary of Product Characteristics; 2016; Actelion Registration Ltd, London, UK. 2. Zavesca® (miglustat) Prescribing Information; 2014; Actelion Pharmaceuticals US Inc; South San Francisco, CA. 3. Patterson MC, et al. *Lancet Neurol*. 2007;6:765-772.

Clinical Studies in NPC are Ongoing

Study Name/Details	Population	Primary Outcome	Start	End	Status	Sponsor
P2/3 Arimoclomol Prospective Study in Patients Diagnosed With Niemann-Pick Disease Type C NCT02612129	Genetically confirmed NPC1/NPC2; age 2-18 years (N=50)	Change in NPC disease severity score	Jun 2016	Jun 2018	Patient recruitment complete	Orphazyme
P1/2 Study of Pharmacokinetics and Preliminary Efficacy of (HP-Beta-CD) in Patients With Niemann-Pick C1 NCT02912793	Confirmed diagnosis NPC1; VSGP; ≥2 years	Pharmacokinetics	Mar 2017	Dec 2018	Recruiting	CTD Holdings, Inc.
P1 Study of the Pharmacokinetics of Trappsol (HP-Beta-CD) and Effects on Potential Biomarkers of Niemann-Pick C1 (NPC1) NCT02939547	NPC1; VSGP; age ≥18 years	Pharmacokinetics	Sept 2017	Dec 2017	Recruiting	CTD Holdings, Inc.

VSGP, vertical supranuclear gaze palsy

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VTS-270

Animal Model Data

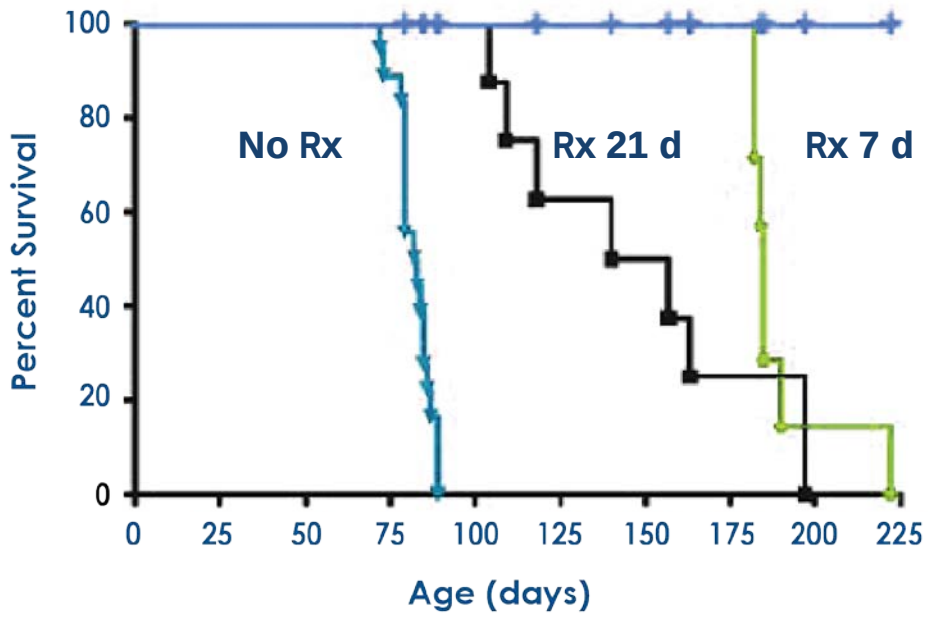
Phase 1/2 Data

Phase 2/3 Program

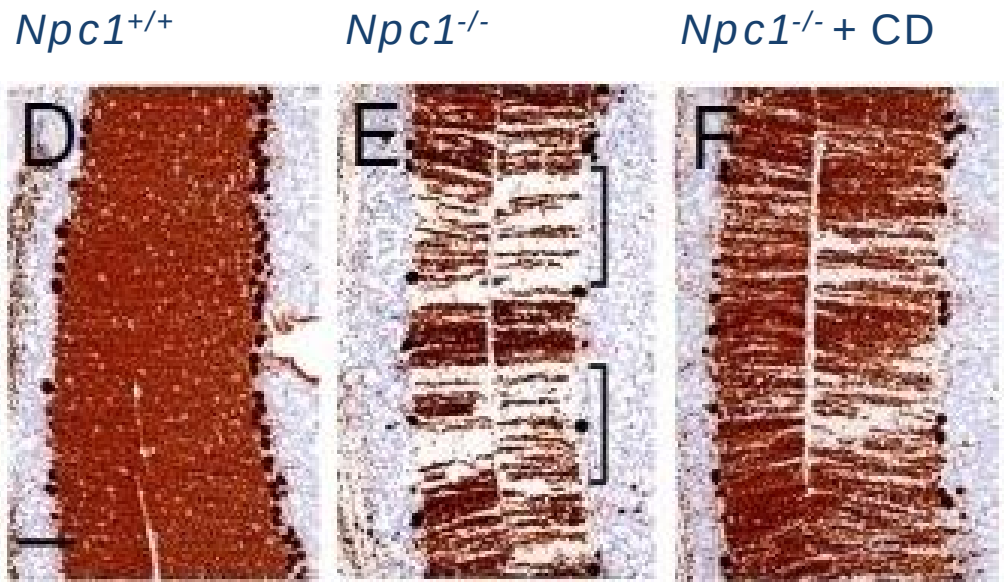
2-Hydroxypropyl-β-Cyclodextrin (HPβCD) Treatment in a Mouse Model Showed Increased Survival

- NPC1 mouse model

Survival[1]



Cerebellar pathology: 49-days[2]



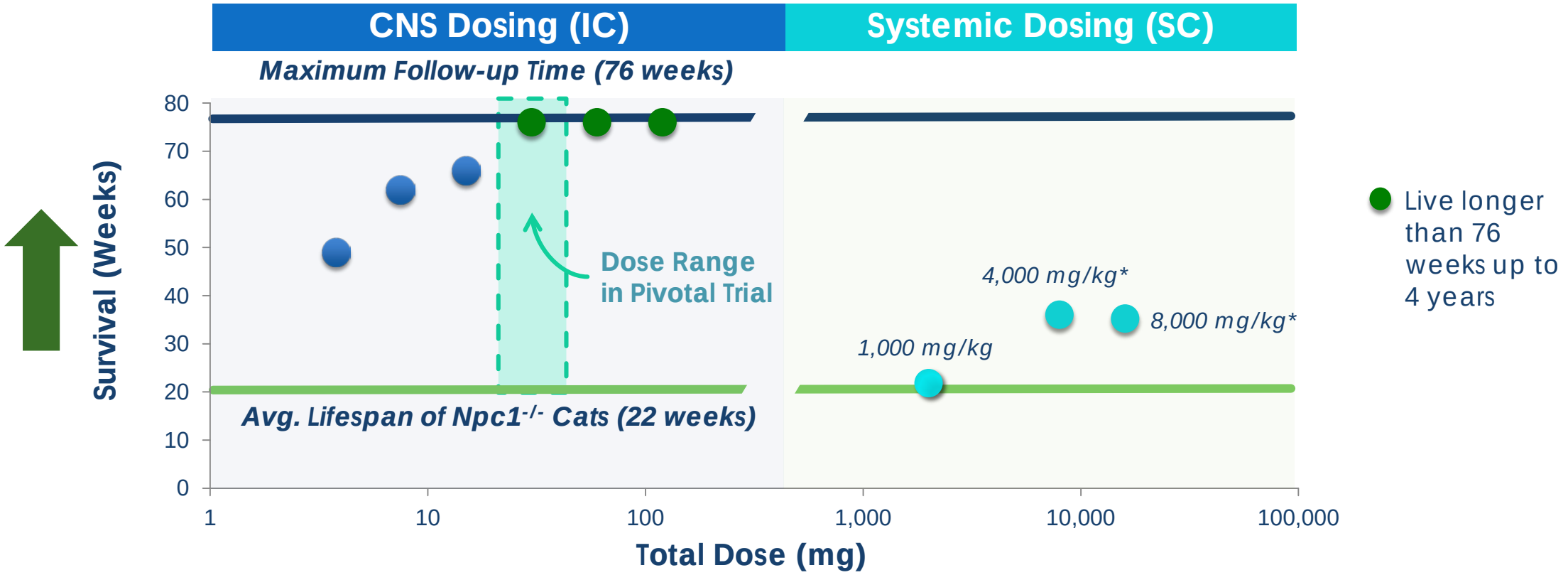
1. Davidson C et al. *PLoS One*. 2009;4:e6951. 2. Liu B et al. *Proc Natl Acad Sci U S A*. 2009;106: 2377-2382.

HPβCD Treatment in a Cat Model Also Showed Improved Function & Survival

- NPC1 cat model
  - 24-week NPC1 mutant cats (HPβCD, miglustat, untreated)

Courtesy of Charles Vite

Where Do You Dose? *CNS Versus Systemic*



*Associated with pulmonary toxicity. CNS, central nervous system; IC, intracisternal; SC, subcutaneously. HPβCD IC administration began at 3 weeks of age, and doses were repeated every 14 days. HPβCD SC administration began at 3 weeks of age and doses were repeated every 7 days.

Vite CH, et al. *Sci Tranl Med.* 2015;7(276):276ra26.

Lancet. 2017 Aug 10.
pii: S0140-6736(17)31465-4. doi: 10.1016/S0140-6736(17)31465-4.

Intrathecal 2-hydroxypropyl-β-cyclodextrin decreases neurological disease progression in Niemann-Pick disease, type C1: a non-randomised, open-label, phase 1–2 trial

Daniel S Ory, Elizabeth A Ottinger, Nicole Yanjanin Farhat*, Kelly A King, Xuntian Jiang, Lisa Weissfeld, Elizabeth Berry-Kravis, Cristin D Davidson, Simona Bianconi, Lee Ann Keener, Ravichandran Rao, Ariane Soldatos, Rohini Sidhu, Kimberly A Walters, Xin Xu, Audrey Thurm, Beth Solomon, William J Pavan, Bernardus N Machielse, Mark Kao, Steven A Silber, John C McKew, Carmen C Brewer, Charles H Vite, Steven U Walkley, Christopher P Austin, Forbes D Porter*

Summary

Background Niemann-Pick disease, type C1 (NPC1) is a lysosomal storage disorder characterised by progressive neurodegeneration. In preclinical testing, 2-hydroxypropyl-β-cyclodextrins (HPβCD) significantly delayed cerebellar Purkinje cell loss, slowed progression of neurological manifestations, and increased lifespan in mouse and cat models of NPC1. The aim of this study was to assess the safety and efficacy of lumbar intrathecal HPβCD.

Published Online
August 10, 2017
http://dx.doi.org/10.1016/
S0140-6736(17)31465-4

See Online/Comment

Study Methods

Intrathecal administration of HPβCD (VTS-270) was investigated in an open-label, dose-escalation phase 1/2a study in patients with NPC, and efficacy (NPC-CSS) was compared with a historical age- and severity-matched historical NIH cohort[1]

Key eligibility criteria[a]

- NPC with neurological manifestations
- Aged 2–25 years
- Body weight >12 kg
- No severe neurological manifestations of NPC

→ **Intrathecal VTS-270**
Dose range: 50–1200 mg administered monthly (n=14)

→ **Intrathecal VTS-270**
Dose range: 200–400 mg administered every 2 weeks (n=3)

Patients aged 4–24 years with ≥2 natural history assessments from an NIH natural history study of 91 patients (NCT00344331)

ENDPOINTS

Primary: Change in 24(S)-HC $AUC_{8\text{-}72}$ with VTS-270 vs saline administration

Secondary: Clinical efficacy (per NNSS[2]) vs age- and severity-matched NIH historical cohort

Additional: Changes in CSF concentrations of FABP3 & calbindin D

Adverse events & audiological assessments[b]

PK (to be reported separately later)

24(S)-HC, 24(S)-hydroxycholesterol; AUC, area under the curve; CSF, cerebrospinal fluid; FABP3, fatty acid binding protein 3; HPβCD, 2-hydroxypropyl-β-cyclodextrin; NIH, National Institutes of Health; NNSS, NPC Neurological Severity Score; NPC, Niemann-Pick disease, type C; NPC-CSS, NPC Clinical Severity Scale; PK, pharmacokinetics; RUMC, Rush University Medical Center.

a Patients also had to be willing to discontinue nonprescription supplements and be willing to participate in all aspects of the study.

b Severity of adverse events graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

1. Ory DS et al. *Lancet*. 2017 Aug 10. pii: S0140-6736(17)31465-4. doi: 10.1016/S0140-6736(17)31465-4. [Epub ahead of print]. 2. Yanjanin NM et al. *Am J Med Genet*. 2009; 53B:132–40.

No Significant Differences in Baseline Demographics & Clinical Characteristics

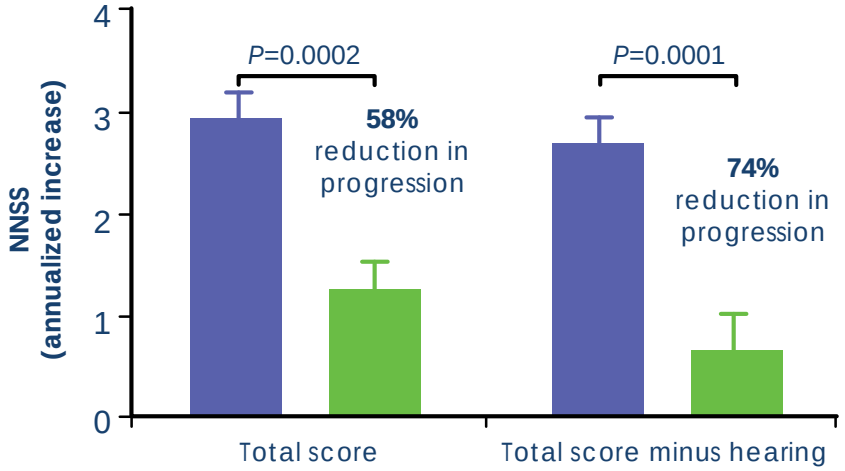
Characteristic	Control cohort n=21	VTS-270 monthly treated cohort n=14	*P* value
Age at baseline, years			
Mean (SEM)	10.7 (6.0)	15.1 (5.5)	0.61
Median (range)	10.0 (4.0-21.9)	14.6 (4.2-23.5)	—
Sex, n (%)			
Male	9 (43)	7 (50)	0.73
Female	12 (57)	7 (50)	—
Total NNSS at baseline			
Mean (SEM)	14.5 (9.7)	19.3 (7.5)	0.72
Median (range)	14 (1-35)	19 (5-32)	—
Total NNSS for hearing at baseline			
Mean (SEM)	13.2 (9.4)	17.0 (7.4)	0.77
Median (range)	12 (1-33)	16 (5-32)	—
Age of first NPC symptom, years			
Mean (SEM)	2.3 (3.7)	3.5 (4.3)	0.83
Median (range)	0.6 (0-13.0)	1.0 (0-12.0)	—
Age of first neurological symptom, years			
Mean (SEM)	5.4 (4.2)	5.9 (3.5)	0.93
Median (range)	3.5 (1.2-15.0)	6.0 (1.0-12)	—
Age of diagnosis, years			
Mean (SEM)	7.1 (6.5)	9.1 (5.6)	0.83
Median (range)	7.0 (0.3-21.0)	9.0 (2.0-20.0)	—
Miglustat use, n (%)			
Yes	16 (76)	12 (86)	0.68
No	5 (24)	2 (14)	—

NNSS, NPC Neurological Severity Score; NPC, Niemann-Pick disease, type C; SEM, standard error of the mean. Ory DS et al. *Lancet*. 2017 Aug 10. pii: S0140-6736(17)31465-4. doi: 10.1016/S0140-6736(17)31465-4. [Epub ahead of print]

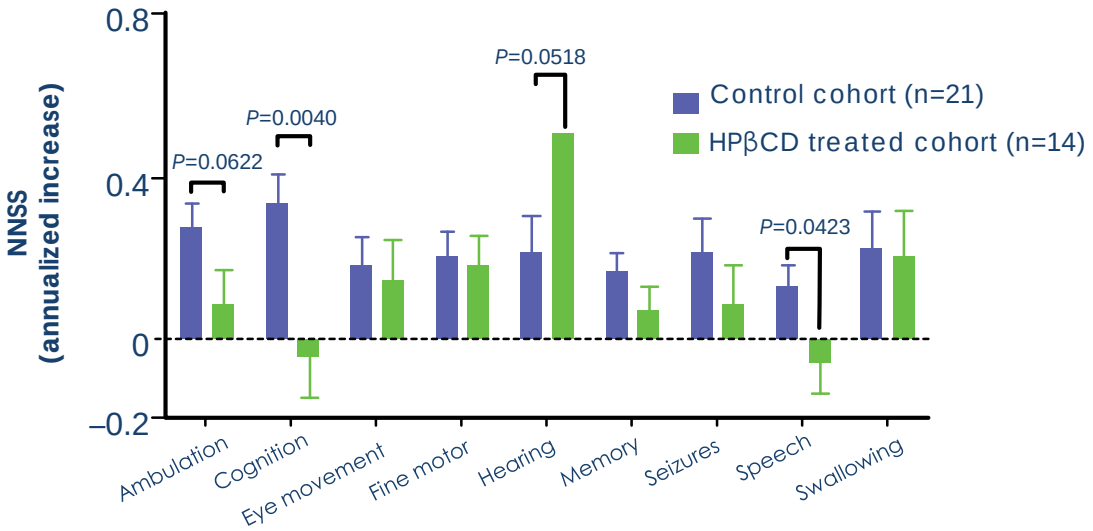
Clinical Efficacy of Intrathecal HPβCD

- Total NNSS for 14 participants treated monthly increased at a slower rate compared with the control cohort even when excluding hearing
- Rate of disease progression decreased for ambulation, cognition, and speech and increased for hearing in participants treated with intrathecal HPβCD compared with the control group

Annualized rate of disease progression in participants treated with intrathecal HPβCD compared with the control group[a]



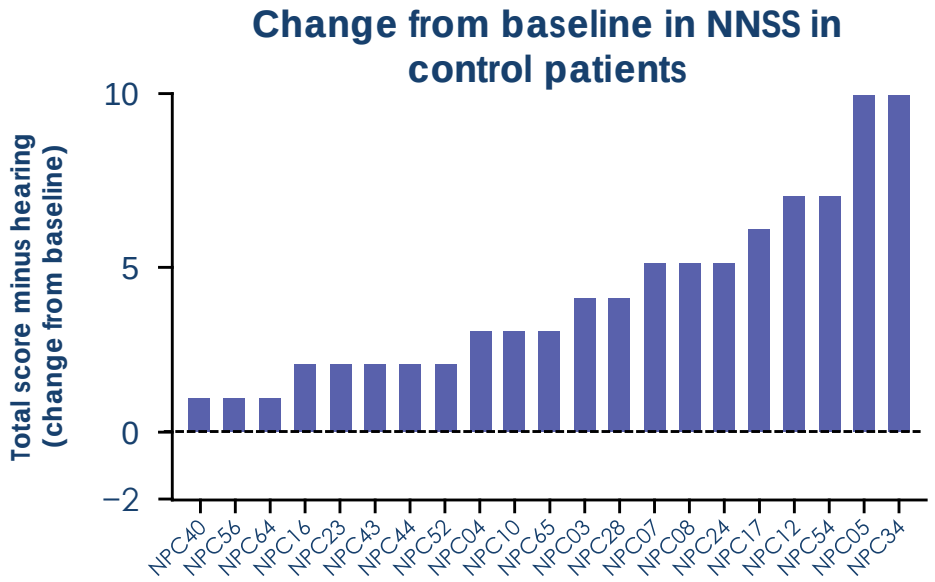
Assessment of the individual major components of the NNSS

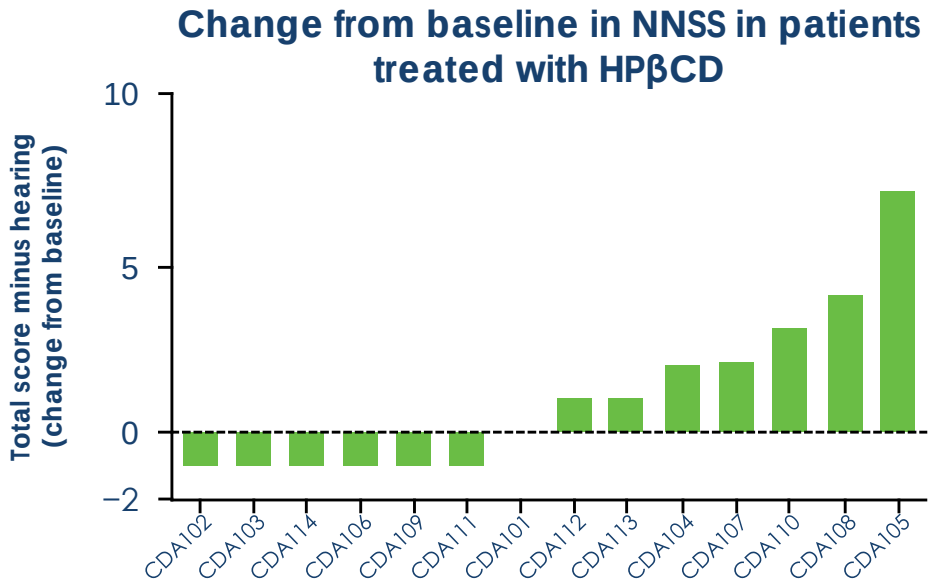


[a]Data are from the 12-month assessment for 3 patients and from the 18-month assessment for 11 patients. HPβCD, 2-hydroxypropyl-β-cyclodextrin; NNSS, NPC Neurological Severity Score; SEM, standard error of the mean. Ory DS et al. *Lancet*. 2017 Aug 10. pii: S0140-6736(17)31465-4. doi: 10.1016/S0140-6736(17)31465-4. [Epub ahead of print]

Clinical Efficacy of Intrathecal HPβCD

- Patients were considered responders if their NNSS minus hearing was stable or improved
- Disease progression was observed in 21 of 21 control patients and in only 7 of 14 participants treated with HPβCD (P=0.0005)





HPβCD, 2-hydroxypropyl-β-cyclodextrin; NNSS, NPC Neurological Severity Score; SEM, standard error of the mean. Ory DS et al. *Lancet*. 2017 Aug 10. pii: S0140-6736(17)31465-4. doi: 10.1016/S0140-6736(17)31465-4. [Epub ahead of print]

Safety: Reported Adverse Events

- No serious adverse drug reactions were observed

Event	NIH subjects N=14	RUMC subjects N=3
Ear and labyrinth events, n (%)		
Sensorineural hearing loss	14 (100)	2 (67)
Tinnitus	6 (43)	1 (33)
Postprocedure complications, n (%)		
Headache	9 (64)	1 (33)
Fatigue	8 (57)	2 (67)
Vomiting	7 (50)	1 (33)
Increased clumsiness, ataxia	5 (36)	1 (33)
Lower back pain	4 (29)	—
Local discomfort at lumbar puncture site	3 (21)	—
Neurological events, n (%)		
Seizure	5 (36)	—
Paresthesia	2 (14)	—
Cough or dysphagia	2 (14)	—

NIH, National Institutes of Health; RUMC, Rush University Medical Center Ory DS et al. *Lancet*. 2017 Aug 10. pii: S0140-6736(17)31465-4. doi: 10.1016/S0140-6736(17)31465-4. [Epub ahead of print]

Safety: Reported Adverse Events (cont'd)

Event	NIH subjects N=14	RUMC subjects N=3
Gastrointestinal/genitourinary events, n (%)		
Transient elevation of liver enzymes	5 (36)	—
Bowel incontinence	4 (29)	—
Diarrhea	3 (21)	1 (33)
Transient proteinuria	2 (14)	—
Transient urobilinogen	2 (14)	—
Nocturia	2 (14)	—
Inflammatory/infectious events, n (%)		
Fever	4 (29)	1 (33)
Otitis media/externa	3 (21)	—
Sinusitis/upper respiratory infection	2 (14)	3 (100)
Infectious enterocolitis	1 (7)	1 (33)
Respiratory events, n (%)		
Aspiration or aspiration pneumonia	2 (14)	—
Laryngospasm during anesthesia	1 (7)	—
Trauma events, n (%)		
Fracture	2 (14)	—
Laceration	—	1 (33)

NIH, National Institutes of Health; RUMC, Rush University Medical Center. Ory DS et al. *Lancet*. 2017 Aug 10. pii: S0140-6736(17)31465-4. doi: 10.1016/S0140-6736(17)31465-4. [Epub ahead of print]

Study Conclusions

- Safety profile of IT VTS-270 acceptable relative to high morbidity and lethality of NPC
- Evidence of biomarker and clinical efficacy VTS-270 treatment associated with decreased disease progression across all major NNSS domains, excluding hearing
- Data accepted by the US Food and Drug Administration to support:
  - Breakthrough therapy designation
  - Development and implementation of randomized, double-blind, sham-controlled, pivotal phase 2b/3 trial

HPβCD, 2-hydroxypropyl-β-cyclodextrin; NNSS, NPC Neurological Severity Score; NPC; Niemann-Pick disease, type C. Ory DS et al. *Lancet*. 2017 Aug 10. pii: S0140-6736(17)31465-4. doi: 10.1016/S0140-6736(17)31465-4. [Epub ahead of print]

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VTS-270 Phase 2/3 Trial

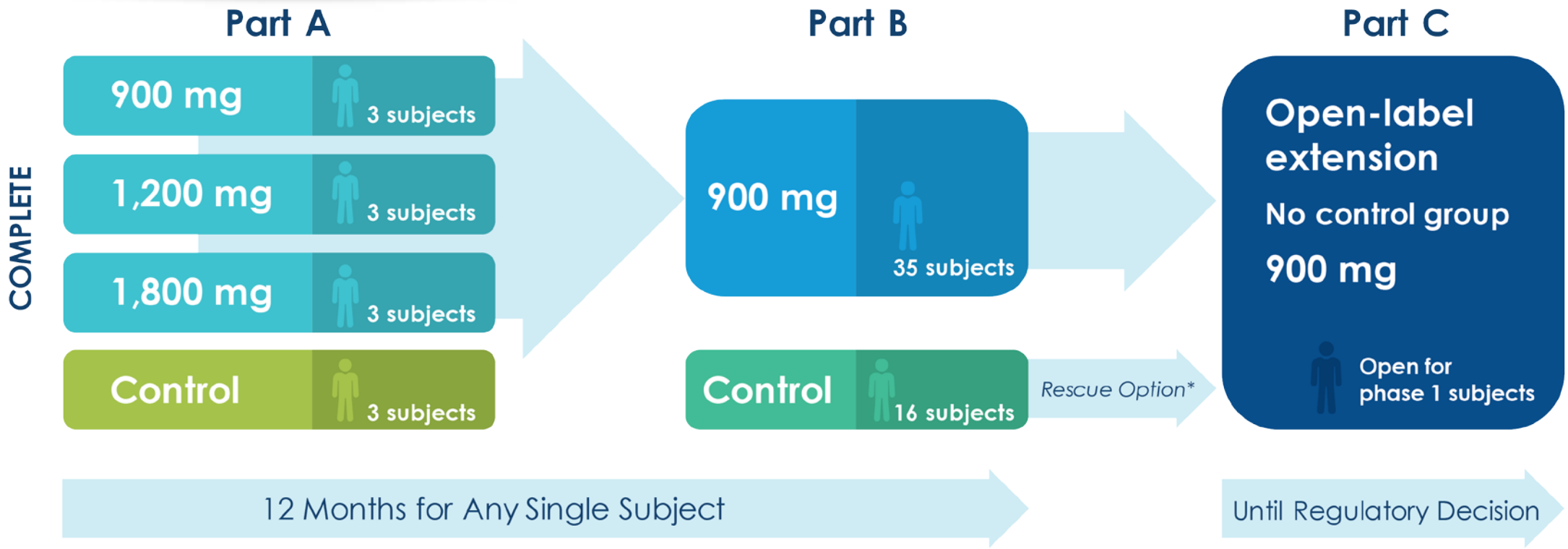
Peter Kiener, D. Phil.

Chief Scientific Officer

Sucampo Pharmaceuticals, Inc.

Global Study Site Distribution

VTS-270 Phase 2b/3 Trial Design



Primary Endpoints: neurologic severity scale and global impression of change; Secondary Endpoints: quality-of-life measures; Safety assessment

*Based on objective criteria.

Key Inclusion Criteria: Parts A and B

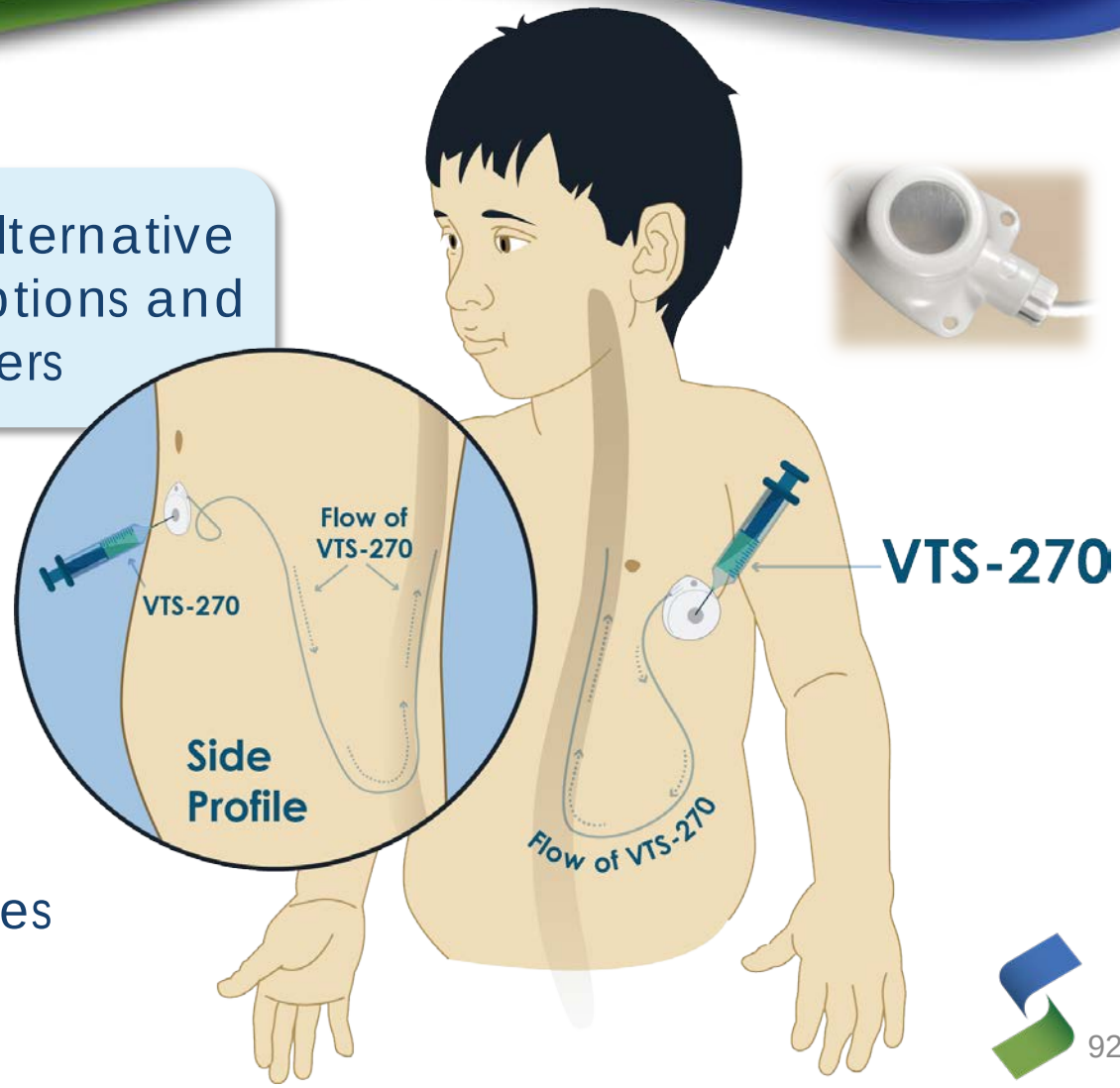
- Male or female subjects, ages 4 to 21 at time of screening with onset of neurological symptoms prior to age 15 years
- Diagnosis of NPC
- Ability to undergo a LP and IT drug administration
  - under monitored anesthesia care (conscious sedation) or if medically necessary, general anesthesia
- NPC Clinical Severity Score with neurological progression in two or more of:
  - ambulation, fine motor skills, or swallowing and cognition
- If taking miglustat, must have been on a stable dose for past 6 months and be willing to remain on a stable dose for the duration of participation in Parts A and B of the study

Intrathecal Access Port Device

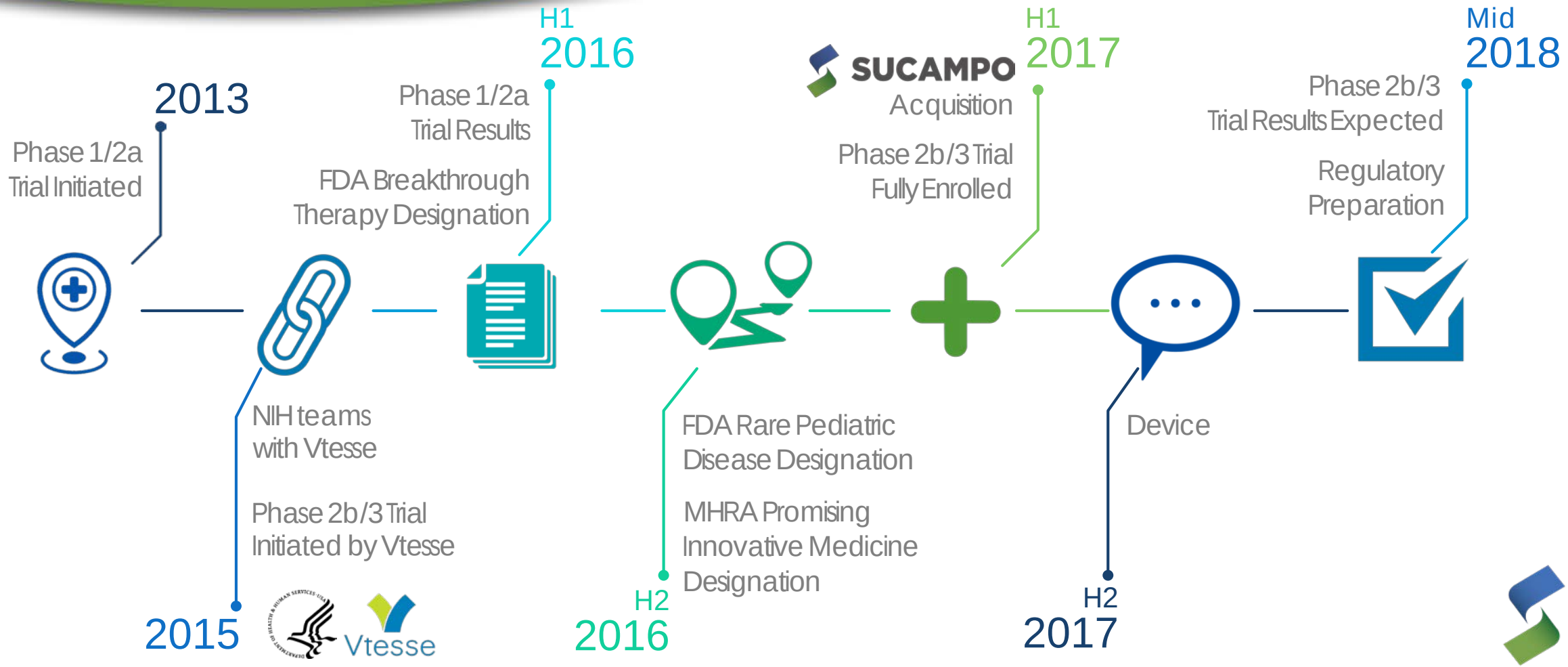
Intrathecal access port device provides an alternative to lumbar punctures for delivery to expand options and convenience for patients and caregivers

Advantages

- Biocompatible
  - Extractable/leachable studies complete
- Resealable septum
  - ~1,500 injections
- Allows patient to continue “normal” activities
- Potentially 5-year implantation life-span



The VTS-270 Development Journey Continues



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Questions & Answers

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Panel Q&A

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Lunch


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Thank You!

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