Stem Cells in Perianal Crohn's Disease (Fistula)

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"Fundación Jimenez Díaz" University Hospital

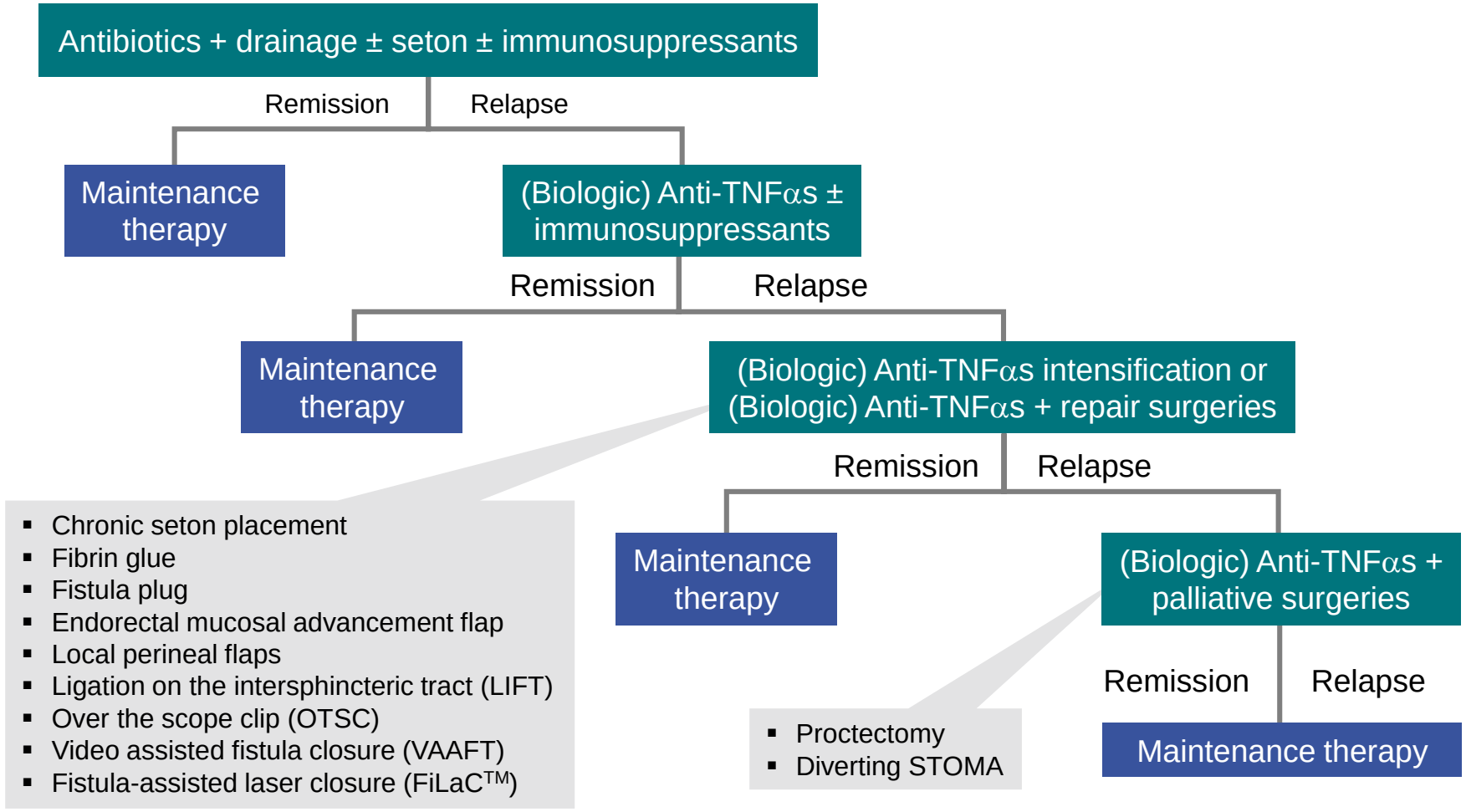
Universidad Autónoma de Madrid

Madrid, Spain

Disclosure

- Member of Advisor Board of TiGenix SAU
- Inventor in a patent “Identification and isolation of multipotent cells from non-osteochondral mesenchymal tissue” (10157355957US), pending to TiGenix
- Inventor in a patent “Use of adipose tissue derived stromal stem cells in treating fistula” (US11/167061), pending to TiGenix
- Consulting fees from Takeda

Algorithm in Crohn's Perianal Fistula
The role of the surgeon



Adapted from Gecse KB, et al. *Gut*. 2014;63:1381-92;

We Need New Perspectives!

Complex Perianal Fistula is Amongst the Highest Unmet need in IBD

- Devastating impact on patients - social, sexual and employment restrictions (Falconi 2002)
- Highly burdensome symptoms: Anal pain and discharge (Mahadev 2011)
- QoL significantly reduced when undergoing repetitive surgical procedures (Riss et al., 2013)
- Anal fistula surgery is an important predictor for fecal incontinence (40% in the overall IBD population) (Norton et al., 2013).
- Patients are highly motivated to avoid complications of fistula:
  - >10% report feeling suicidal
  - Willing to trade 6.5% of life expectancy for cure (Mahadev et al., 2011)

Help-Seeking for Fecal Incontinence in People With Inflammatory Bowel Disease

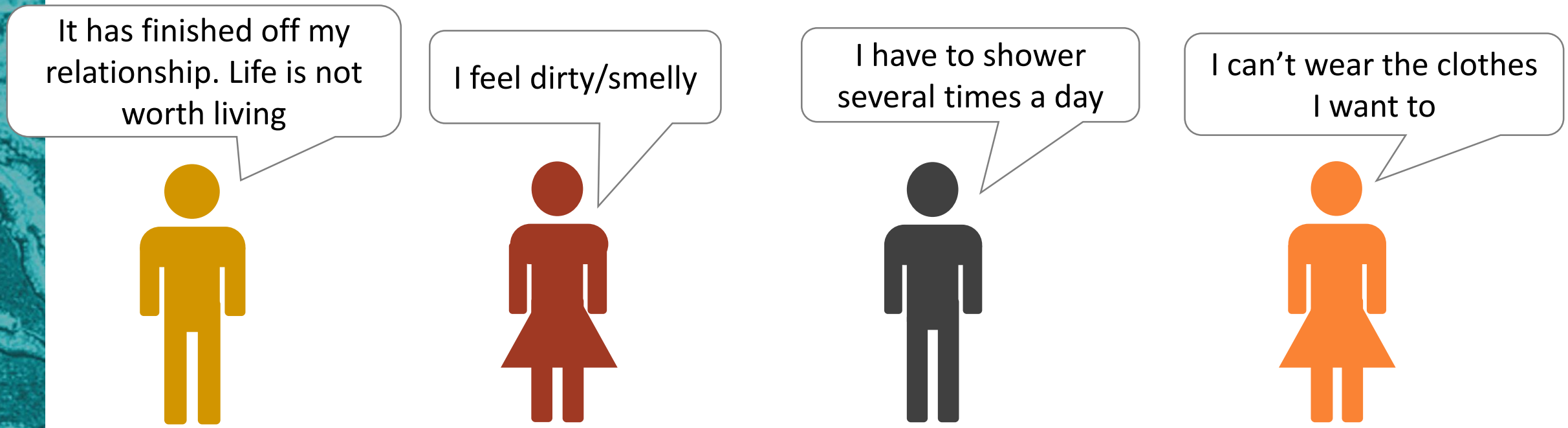
Norton, Christine; Dibley, Lesley

Journal of Wound Ostomy & Continence Nursing: November/December 2013 - Volume 40 - Issue 6 - p 631–638
doi: 10.1097/WON.0b013e3182a9a8b5
Continence Care

We Need New Perspectives!

Patient QoL – the heavy burden of perianal fistulas in CD

- **Fistulas may occur in up to 25% of patients with CD[1]**
- **73% of patients with perianal fistulas in CD report depression[2]**
- **13% of patients with perianal fistulas in CD report suicidal thoughts[2]**



CD: Crohn's disease; QoL: quality of life.

1. Chaparro M, et al. *Gastroenterol*. 2011;140:S-736; 2. Mahadev S, et al. *Colorectal Dis*. 2012;14:331–5.

The fistula Dilemma

RECURRENCE

INCONTINENCE

COMPARISON AMONG CURRENT SURGICAL PROCEDURES IN CD ANAL FISTULA

	RECURRENCE	INCONTINENCE	TECHNICAL DIFFICULTY	POSTOP PAIN
INTO FISTULA TRACTS • Fibrin glue , Plug • FilaC, VAAFT,…	+++	–	–	–
SETON	+++	+	–	++/+
FLAPS	++	++	+++	++
SPHINCTEROPLASTY	+	+++	+++	++
LIFT	+++	+	+++	+
IDEAL TECHNIQUE	–	–	–	–

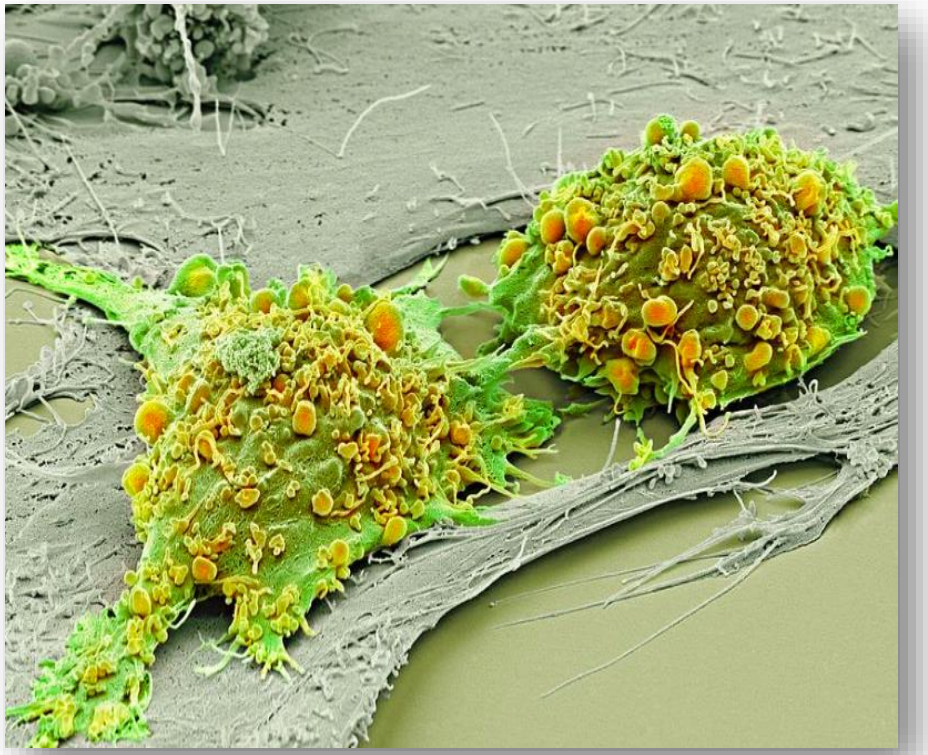
No risk	-
Lower	+
Intermediate	++
High	+++

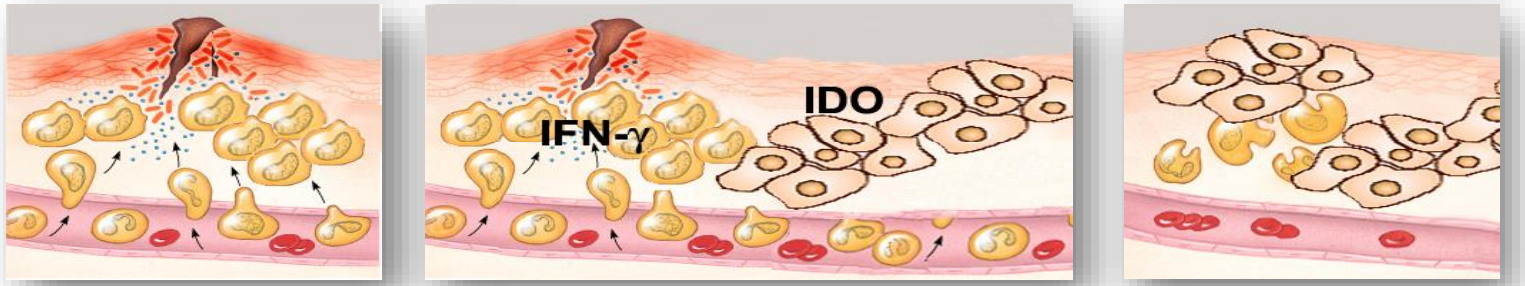
A personal evaluation.
Prof. Garcia-Olmo, Colorectal Surgeon since 1989

May Stem Cells provide a effective procedure like a “Minimally Invasive Surgery”, easy to perform, and without Incontinence risk?

How do we expect cells work in Crohn's Fistula?

- An inmunomodulator effect of adipose derived stem cells has been described.
- These immunosuppressive properties lead to a potent anti-inflammatory effect





A

Inflammation

- Infiltration of lymphocytes (PBLs) in wound area
- Secretion of pro-inflammatory cytokines
- Sensation of pain

B

Delivery of eASCs

- Activation of eASC by a cytokine called IFN-γ
- Expression of an enzyme called IDO by eASCs
- Suppression of the proliferation of activated PBLs
- Suppression of production of inflammatory signals

C

Healing

- Elimination of activated PBLs
- Abrogation of pro-inflammatory cytokines
- Cessation of pain
- Repair of tissue

Mechanism of Action of ASCs

- ASCs are activated in an inflamed environment
- Activated ASCs suppress the proliferation of lymphocytes and suppress the inflammation
- Local treatment of inflammatory diseases with tissue damage/ wounds: ASCs act at the source of the inflammation and establish an environment that will permit a healing
- Systemic treatment of diseases with acute inflammatory component: ASCs migrate to the inflammatory environment and suppress inflammation, avoiding tissue damage

Mesenchymal stem cells inhibit lymphocyte proliferation by mitogens and alloantigens by different mechanisms

Ida Rasmusson[a,*], Olle Ringdén[a,b], Berit Sundberg[a], Katarina Le Blanc[a,b]

Leukemia (2005), 1–8
© 2005 Nature Publishing Group All rights reserved 0887-6924/05 $30.00
www.nature.com/leu

Mesenchymal stem cells induce apoptosis of activated T cells

J Plumas[1,3], L Chaperot[1,3], M-J Richard[2,3], J-P Molens[1,3], J-C Bensa[1,3] and M-C Favrot[2,3]

[1]Etablissement Français du Sang Rhône-Alpes, Grenoble, France; [2]Centre d'innovation en biologie, Centre Hospitalier Universitaire Michallon, Grenoble, France; and [3]Unité Mixte de Thérapie Cellulaire et Tissulaire, Grenoble, France

TRANSPLANTATION

Human mesenchymal stem cells modulate allogeneic immune cell responses

Sudeepta Aggarwal and Mark F. Pittenger

bjh research paper

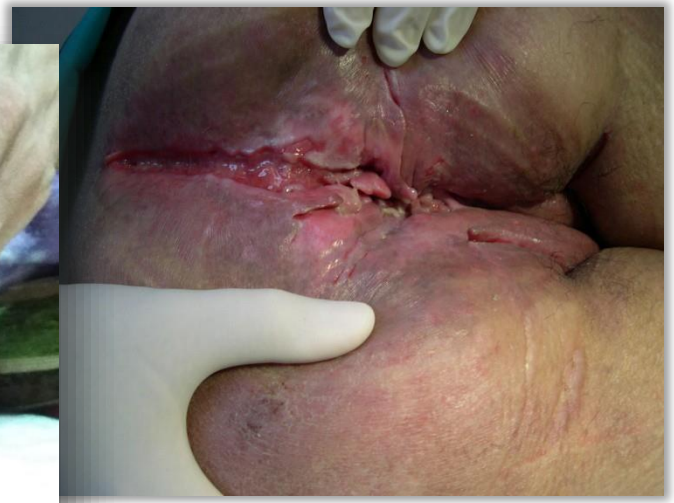
Immunomodulatory effect of human adipose tissue-derived adult stem cells: comparison with bone marrow mesenchymal stem cells

STEM CELLS®
Translational and Clinical Research

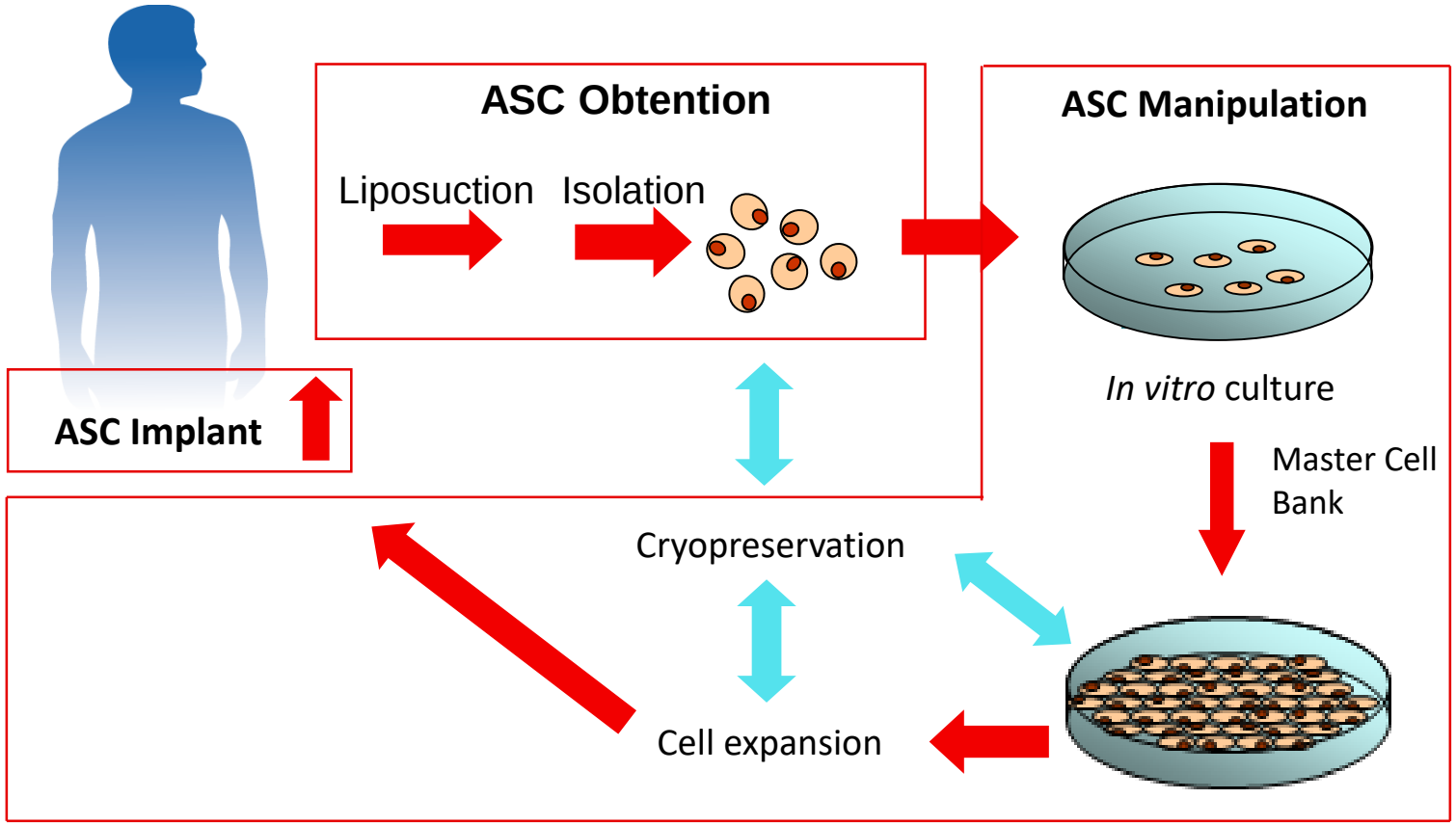
Role for Interferon-γ in the Immunomodulatory Activity of Human Bone Marrow Mesenchymal Stem Cells

Fistulas in Crohn's disease: A real problem of inflammation and wound healing

- Perianal discharge
- Pain
- Swelling
- Bleeding
- Diarrhoea
- Skin excoriation
- External opening
- …and SETON is the HERO!



Technologies involved in Adipose Derived Stem Cells



Mesenchymal stem cells for fistulising Crohn's disease: "The long and winding road" from the bench to the bedside.

Mesenchymal cells in perianal fistulas

Garcia-Olmo (1)
Autologous
Case report

Garcia-Olmo (4)
Autologous
Phase 1
Single arm

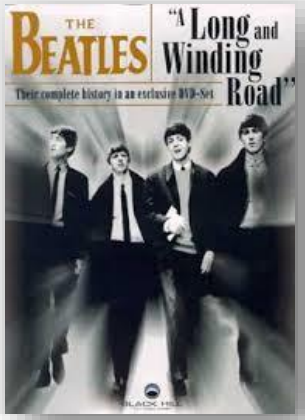
Garcia-Olmo (14)
Autologous
Phase 2b
Open label
MSC in fibrin glue

Garcia-Olmo (1)
Allogeneic
Case Report

de la Portilla (24)
Allogeneic
Phase 1/2a
Single arm

Panes (212)
Allogeneic Phase 3 RCT
Allogeneic Phase 3 Long-Term

2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017



Ciccocioppo (10)
Autologous
Bone marrow
Single arm

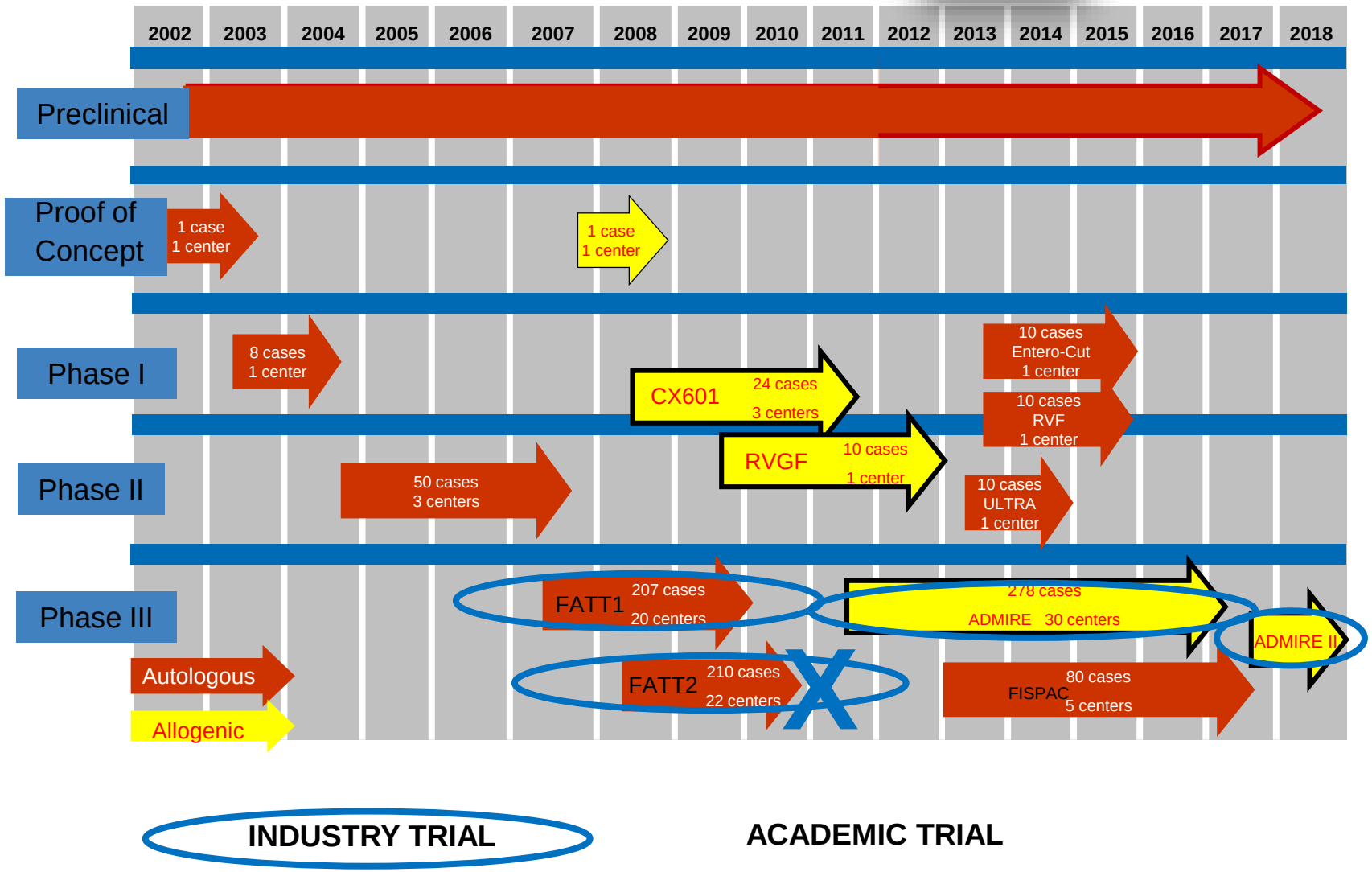
Lee (33)
Autologous
Phase 2
Single arm

Cho (10)
Autologous
Phase 1

Molenkijk (21)
Allogeneic
Bone marrow
4 arms

Lightner, A. L. & Faubion, W. A. Mesenchymal Stem Cell Injections for the Treatment of Perianal Crohn's Disease: What We Have Accomplished and What We Still Need to Do. *J Crohns Colitis* **11,** 1267–1276 (2017).

ASC Clinical Development in fistula

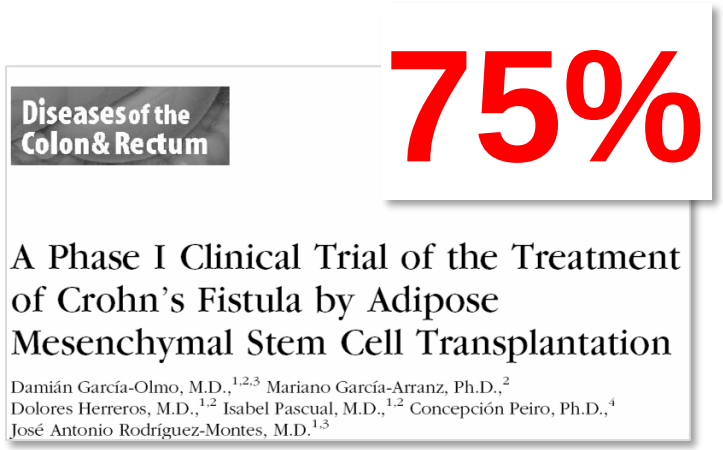


INDUSTRY TRIAL

ACADEMIC TRIAL

Autologous ASCs: Phase 1 and 2 studies

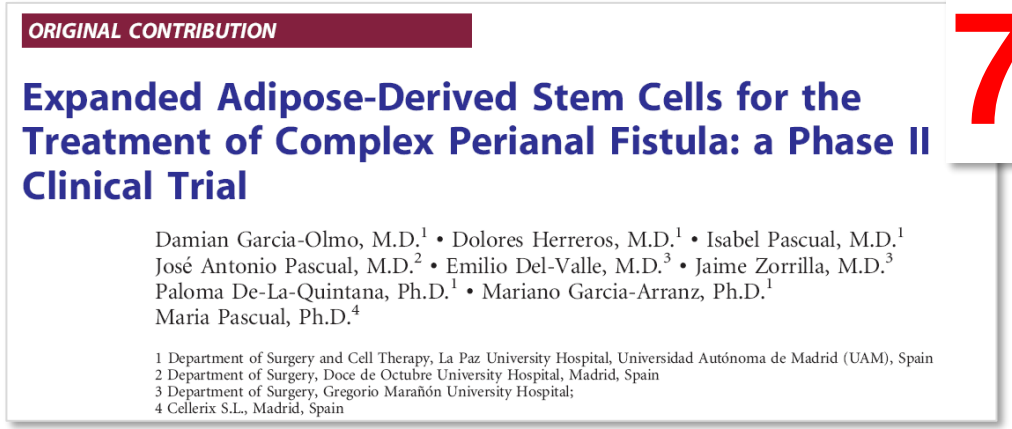
Administration of autologous ASCs was effective in inducing healing in patients with complex Crohn's perianal fistula, and this procedure can be considered safe


Diseases of the Colon & Rectum

A Phase I Clinical Trial of the Treatment of Crohn's Fistula by Adipose Mesenchymal Stem Cell Transplantation

Damián García-Olmo, M.D.,[1,2,3] Mariano García-Arranz, Ph.D.,[2] Dolores Herreros, M.D.,[1,2] Isabel Pascual, M.D.,[1,2] Concepción Peiro, Ph.D.,[4] José Antonio Rodríguez-Montes, M.D.[1,3]

75%

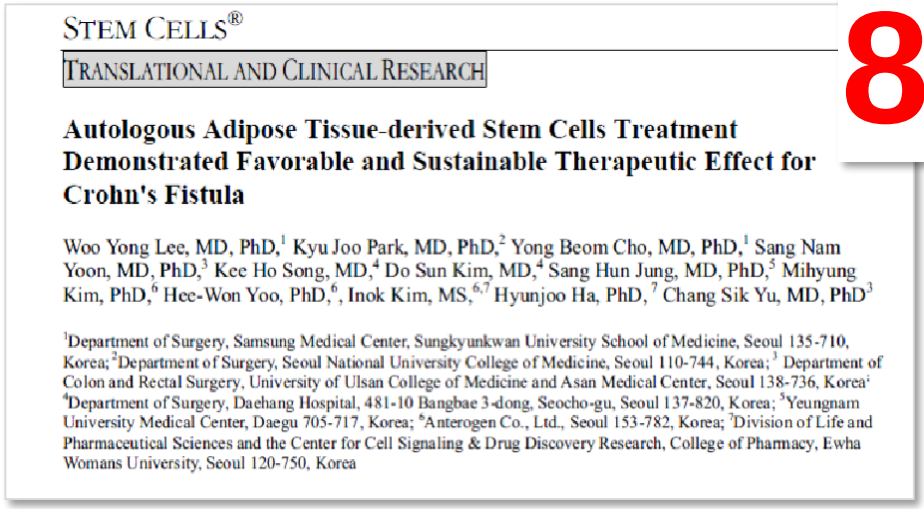

ORIGINAL CONTRIBUTION

Expanded Adipose-Derived Stem Cells for the Treatment of Complex Perianal Fistula: a Phase II Clinical Trial

Damian Garcia-Olmo, M.D.[1] • Dolores Herreros, M.D.[1] • Isabel Pascual, M.D.[1] José Antonio Pascual, M.D.[2] • Emilio Del-Valle, M.D.[3] • Jaime Zorrilla, M.D.[3] Paloma De-La-Quintana, Ph.D.[1] • Mariano Garcia-Arranz, Ph.D.[1] Maria Pascual, Ph.D.[4]

1 Department of Surgery and Cell Therapy, La Paz University Hospital, Universidad Autónoma de Madrid (UAM), Spain
2 Department of Surgery, Doce de Octubre University Hospital, Madrid, Spain
3 Department of Surgery, Gregorio Marañón University Hospital;
4 Cellerix S.L., Madrid, Spain

70%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TRANSLATIONAL AND CLINICAL RESEARCH

Autologous Adipose Tissue-derived Stem Cells Treatment Demonstrated Favorable and Sustainable Therapeutic Effect for Crohn's Fistula

Woo Yong Lee, MD, PhD,[1] Kyu Joo Park, MD, PhD,[2] Yong Beom Cho, MD, PhD,[1] Sang Nam Yoon, MD, PhD,[3] Kee Ho Song, MD,[4] Do Sun Kim, MD,[4] Sang Hun Jung, MD, PhD,[5] Mihyung Kim, PhD,[6] Hee-Won Yoo, PhD,[6], Inok Kim, MS,[6,7] Hyunjoo Ha, PhD, [7] Chang Sik Yu, MD, PhD[3]

[1]Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 135-710, Korea; [2]Department of Surgery, Seoul National University College of Medicine, Seoul 110-744, Korea; [3] Department of Colon and Rectal Surgery, University of Ulsan College of Medicine and Asan Medical Center, Seoul 138-736, Korea; [4]Department of Surgery, Daehang Hospital, 481-10 Bangbae 3-dong, Seocho-gu, Seoul 137-820, Korea; [5]Yeungnam University Medical Center, Daegu 705-717, Korea; [6]Anterogen Co., Ltd., Seoul 153-782, Korea; [7]Division of Life and Pharmaceutical Sciences and the Center for Cell Signaling & Drug Discovery Research, College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea

82%

Red texts indicate the percentage of patients with complete fistula healing.

1. García-Olmo D, et al. *Dis Colon Rectum.* 2005;48:1416-23. 2. Garcia-Olmo D, et al. *Dis Colon Rectum.* 2009;52:79-86. 3. Lee WY, et al. *Stem Cells.* 2013;31:2575-81.

Good tolerability of ASCs and feasibility of allogeneic cell therapy

- ASCs are considered “immune privileged” because of:[1-3]
  - Low expression of HLA I (constitutively)
  - Lack of expression of HLA II (constitutively)
  - Lack of expression of classic co-stimulatory molecules (after priming)
  - Low expression of ligands for NK cell receptors (constitutively or after priming)
  - Delay of the maturation of terminally differentiated effector T cells

- Anergy of T lymphocytes and immune tolerance
- Delayed or reduced activation of the innate and adaptive immune responses

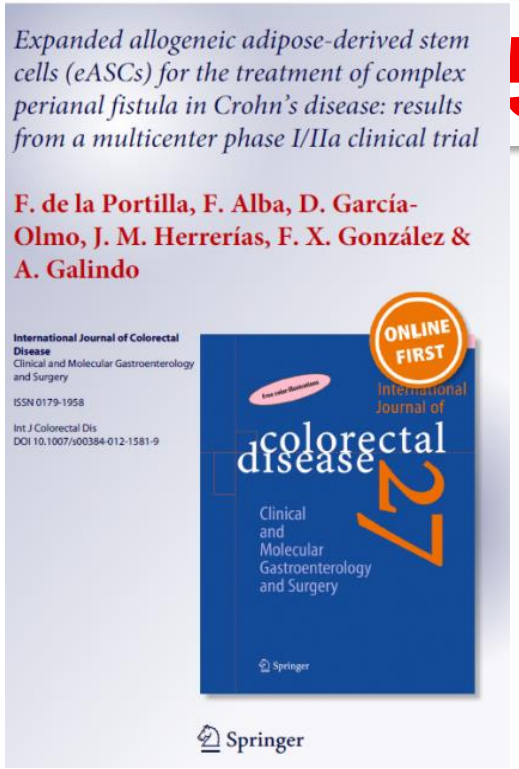
- Feasibility of allogeneic treatments without suppression of host immunity
  - Easily available cell therapy
  - Economically affordable

ASC, Adipose-derived mesenchymal stem cells. BM, bone marrow. HLA, human leukocyte antigen. MSC, mesenchymal stem cells. NK cell, natural killer cell.

1. de la Portilla F, *et al. Int J Colorectal Dis.* 2013;28:313-23. 2. DelaRosa O, et *al. Stem Cells Dev.* 2012;21:1333-43. 3. Ghannam S, *et al*. *J Immunol.* 2010;185:302-12.

Allogenic ASCs: phase 1 and phase 2 studies

Administration of Allogenic ASCs was effective in inducing healing in patients with complex Crohn's perianal fistula, and this procedure can be considered safe



53%

57%

Gastroenterology

0, 117, 125

EDITORIALS

Cumulative Evidence That Mesenchymal Stem Cells Promote Healing of Perianal Fistulas of Patients With Crohn's Disease–Going From Bench to Bedside

Reprint requests
Address requests for reprints to: Damian Garcia-Olmo, MD, Department of Surgery (Fundacion Jimenez Diaz), Universidad Autonoma de Madrid, Reyes Católicos 2, 28040 Madrid, Spain. e-mail: damian.garcia@uam.es.

Most current article

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0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2015.08.038

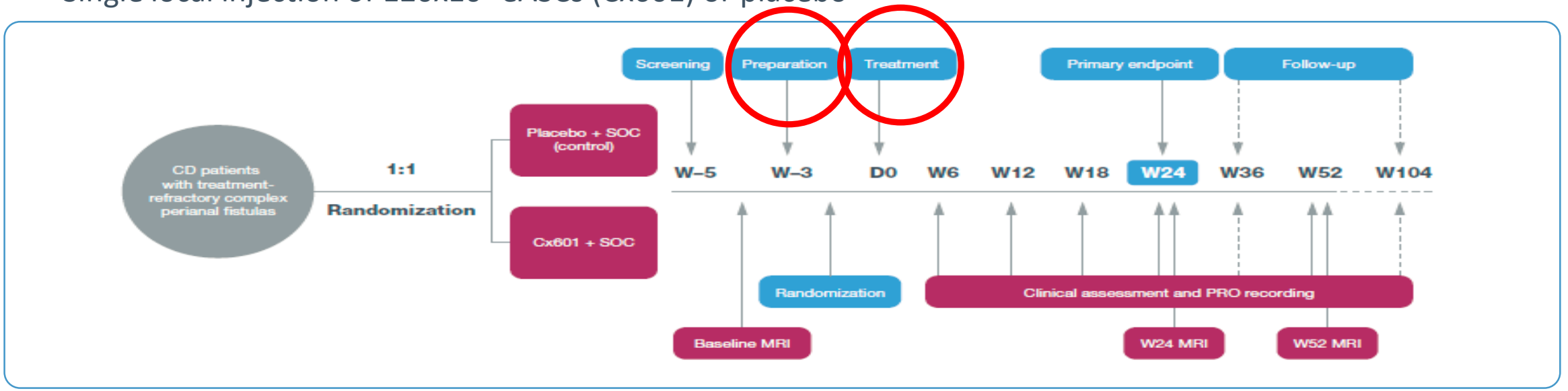
Designing a clinical trial process

- Phase 1: Screening for safety
- Phase 2: Establishing the efficacy of the drug, usually against a placebo
- Phase 3: Final confirmation of safety and efficacy
- Phase 4: Sentry studies during sales

Expanded allogenic ASCs (Cx601): ADMIRE-CD a phase 3 clinical trial in Crohn's perianal fistulas

Adipose Derived Mesenchymal Stem Cells for Induction and Maintenance of Remission in Perianal Fistulizing Crohn's Disease (ADMIRE-CD)

- Double-blind, placebo-controlled, randomized, multicenter, phase 3 study (NCT01541579)
- Single local injection of $120x10^6$ eASCs (Cx601) or placebo



Primary endpoint:

- **Combined remission at week 24:** clinical assessment of closure of all treated external openings that were draining at baseline, and absence of collections >2 cm of the treated perianal fistulas confirmed by masked central MRI

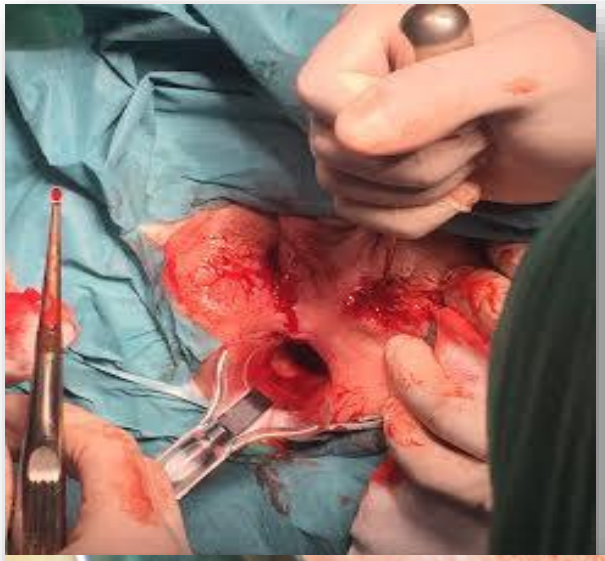
Key secondary endpoints:

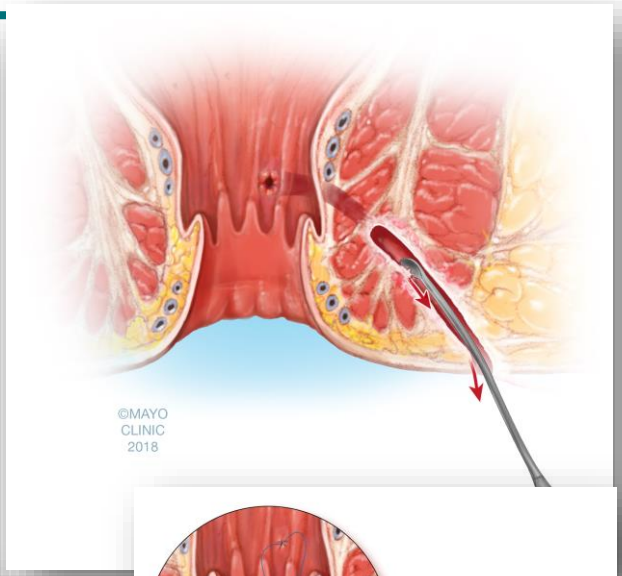
- Clinical remission and response at Weeks 24 and 52
- Combined remission at Week 52

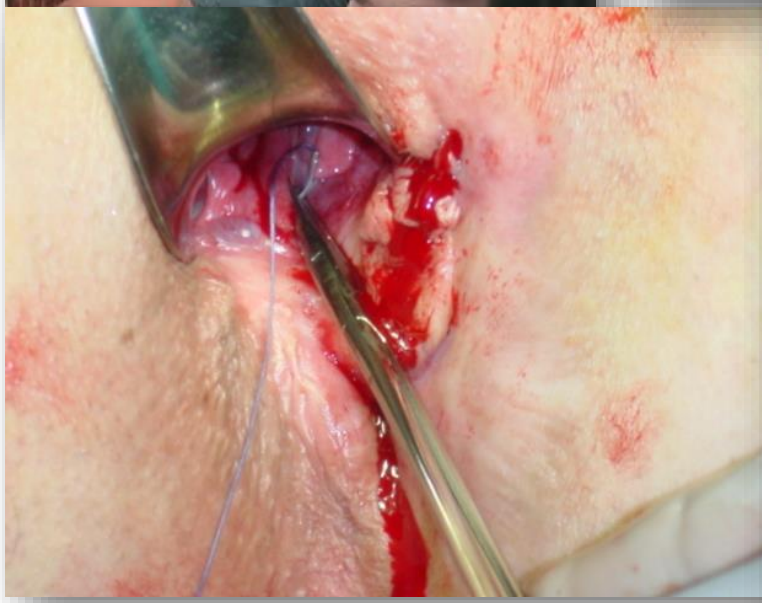
Clinical assessment of closure: absence of draining despite gentle finger compression. Clinical remission: closure of all treated external openings that were draining despite gentle finger compression. Response: closure of ≥50% of all treated external openings that were draining at baseline,
eASC, expanded allogeneic adipose-derived stem cells; MRI, magnetic resonance imaging`; R, randomization.
Panés, J. *et al*. Lancet. 388: 1281-90 (2016).

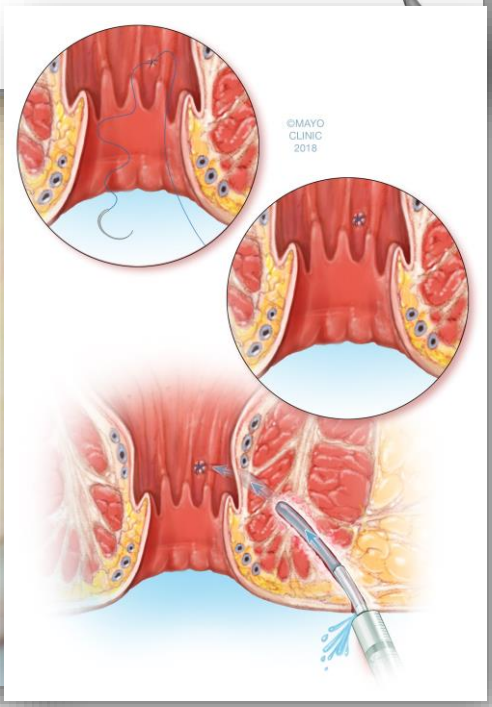
The concept of “Minimally Invasive Surgery” Surgical technique include…

1. Vigorous curettage of all tracts, especially in the IO area
2. Closure of the IO with absorbable, 2-3/0 stitches



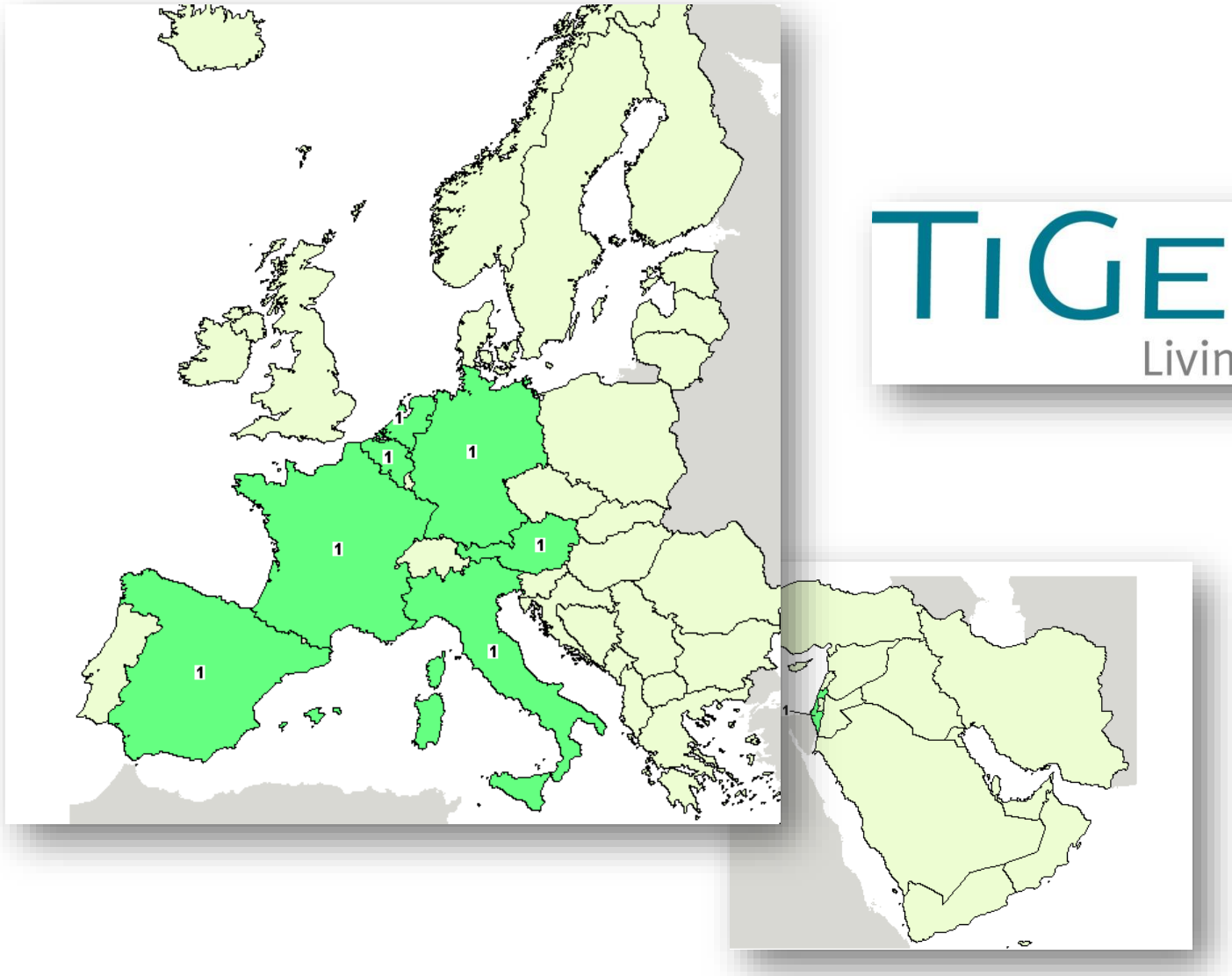






52 Centers at 8 Countries

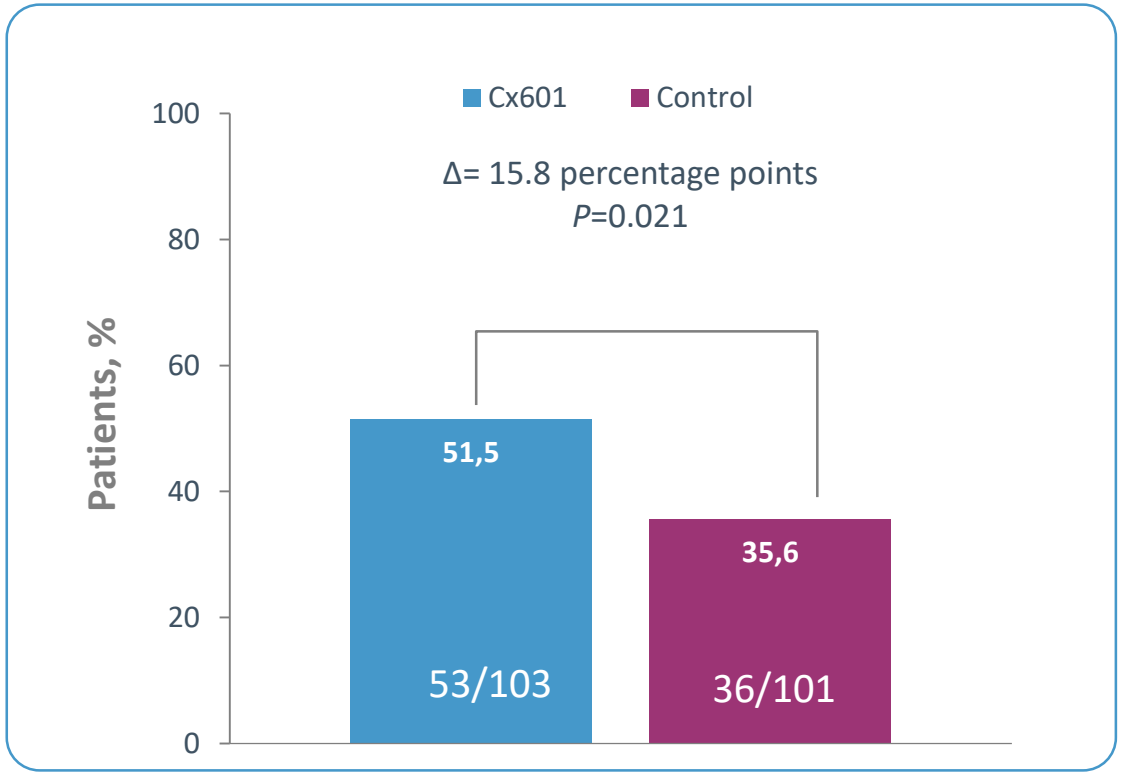
ADMIRE CD study design/objective



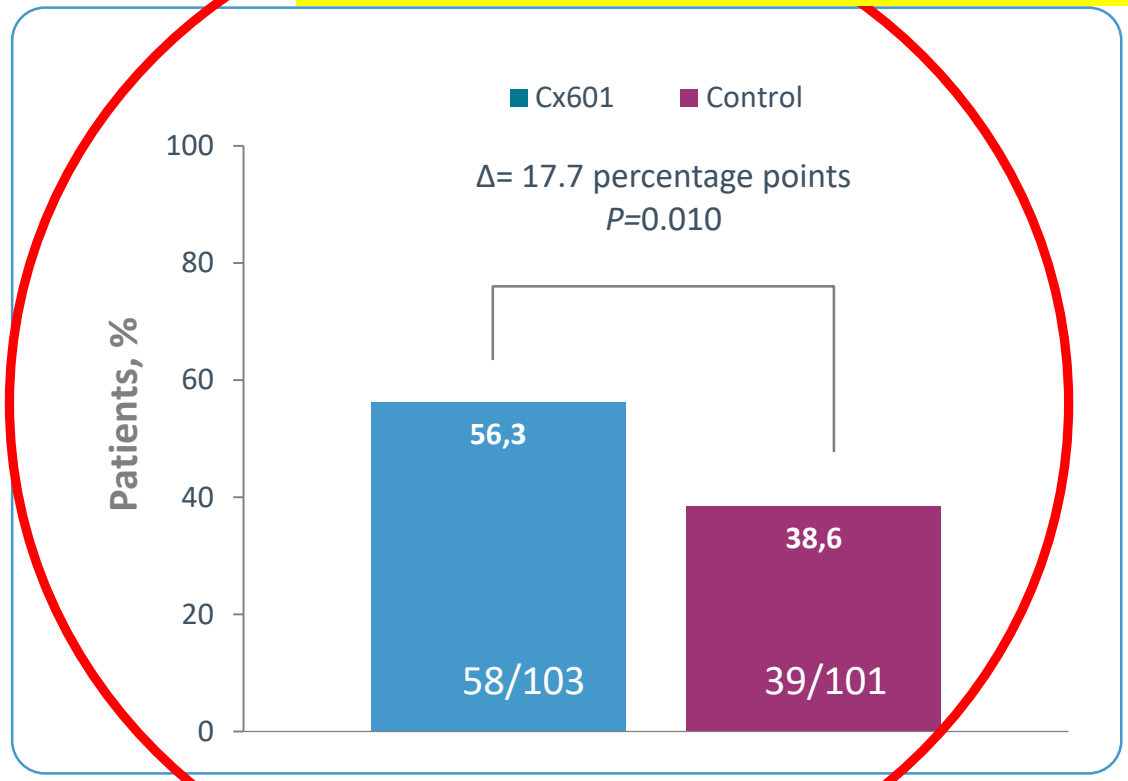
TiGENIX
Living Medicines

Combined remission (Clinical and MRI)* (mITT population, N= 204)

Week 24[1]



Week 52[2]



"Living medicament"

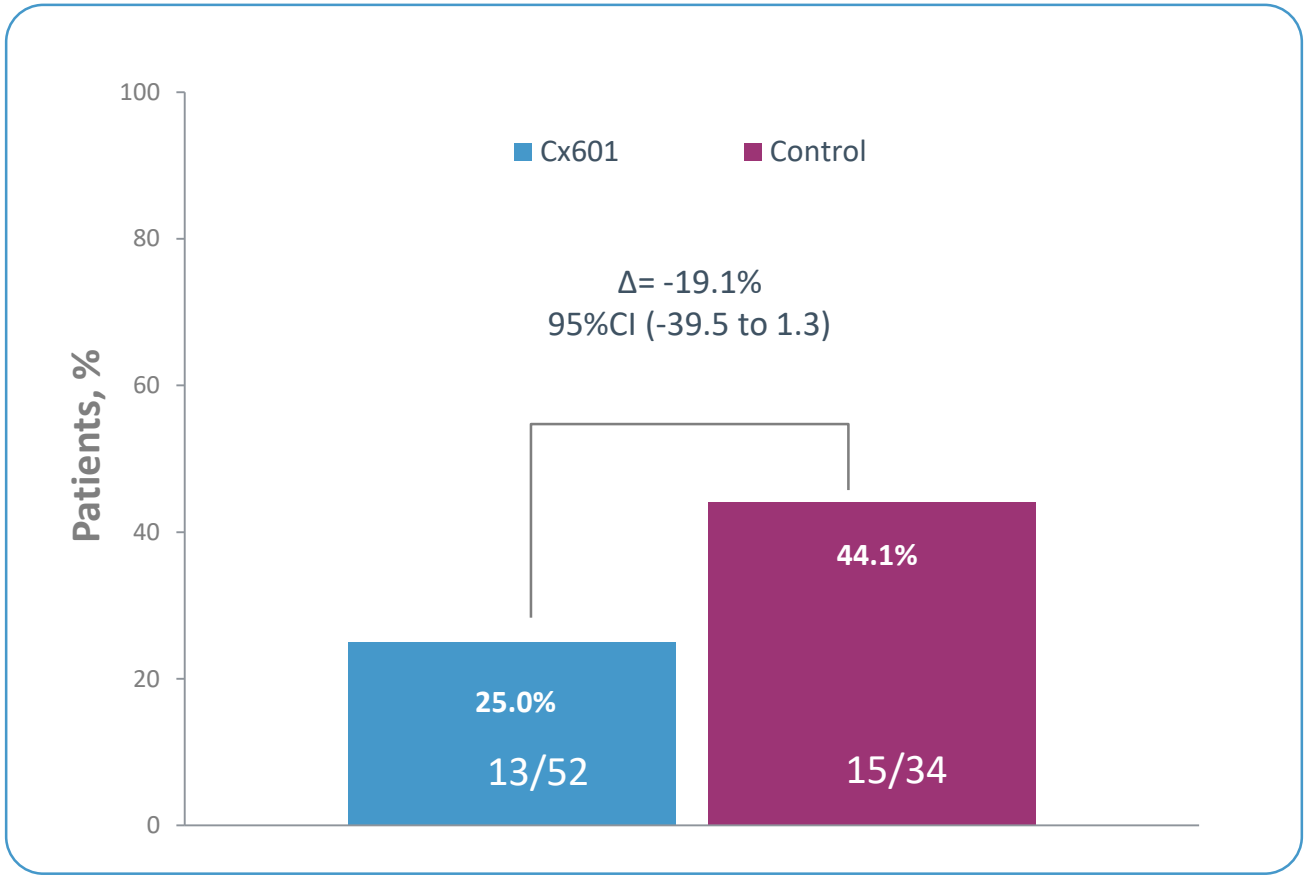
- Data at week 24 and 52 suggest that Cx601 superior to control arm in achieving combined remission
- Difference at week 52 is maintained from week 24 analysis

*Closure of all treated external openings that were draining at baseline assessed clinically, and absence of collections >2 cm in the area of the treated perianal fistulas by blinded central MRI reading.
CI, confidence interval; mITT, modified intention-to-treat (randomized, treated and ≥1 post-baseline efficacy assessment); MRI, magnetic resonance imaging.

1. Panés, J. *et al.* Lancet. 388:1281-90 (2016);. 2. Panés, J. *et al*. Gastroenterology. 2018;154:133 4-1342

Patients with relapse* at week 52 (ITT population – patients with combined remission at week 24)

No combined remission at week 52 in patients with combined remission at week 24 (No LOCF)



*Reopening of any of the treated external openings with active drainage as clinically assessed, or development of a perianal collection > 2cm of the treated perianal fistulae confirmed by centrally blinded MRI assessment in patients with clinical remission at a previous visit combined remission at week 24

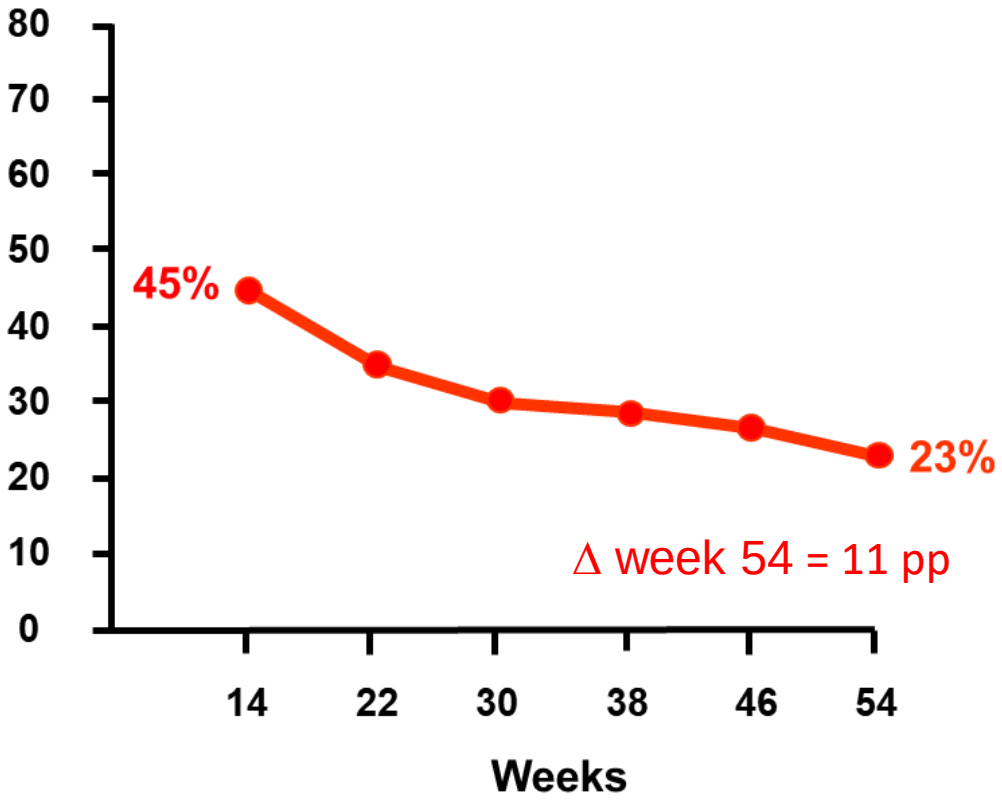
LOCF, Last observation carried forward.

ITT, intent-to-treat.

García-Olmo, D. *et al*. ECCO. Poster P691 (2018).

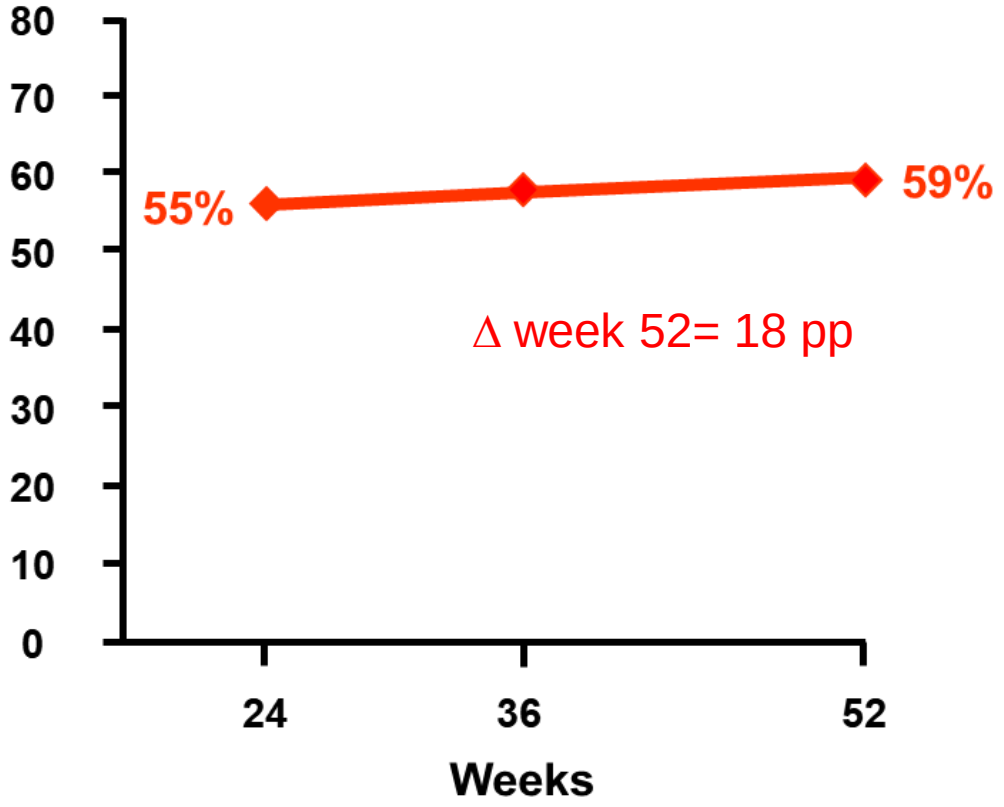
No Drainage after treatment

Infliximab (ACCENT II) [1]



[1]Sands et al 2004

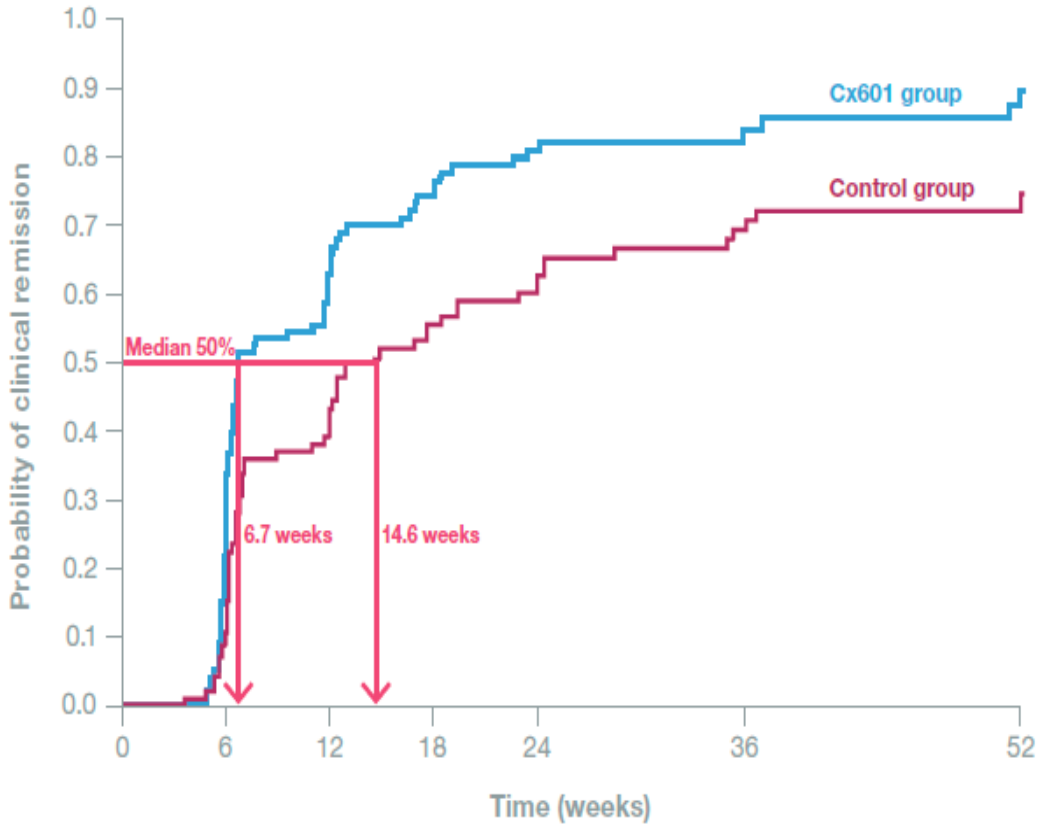
Darvadstrocel (ADMIRE CD) [2]



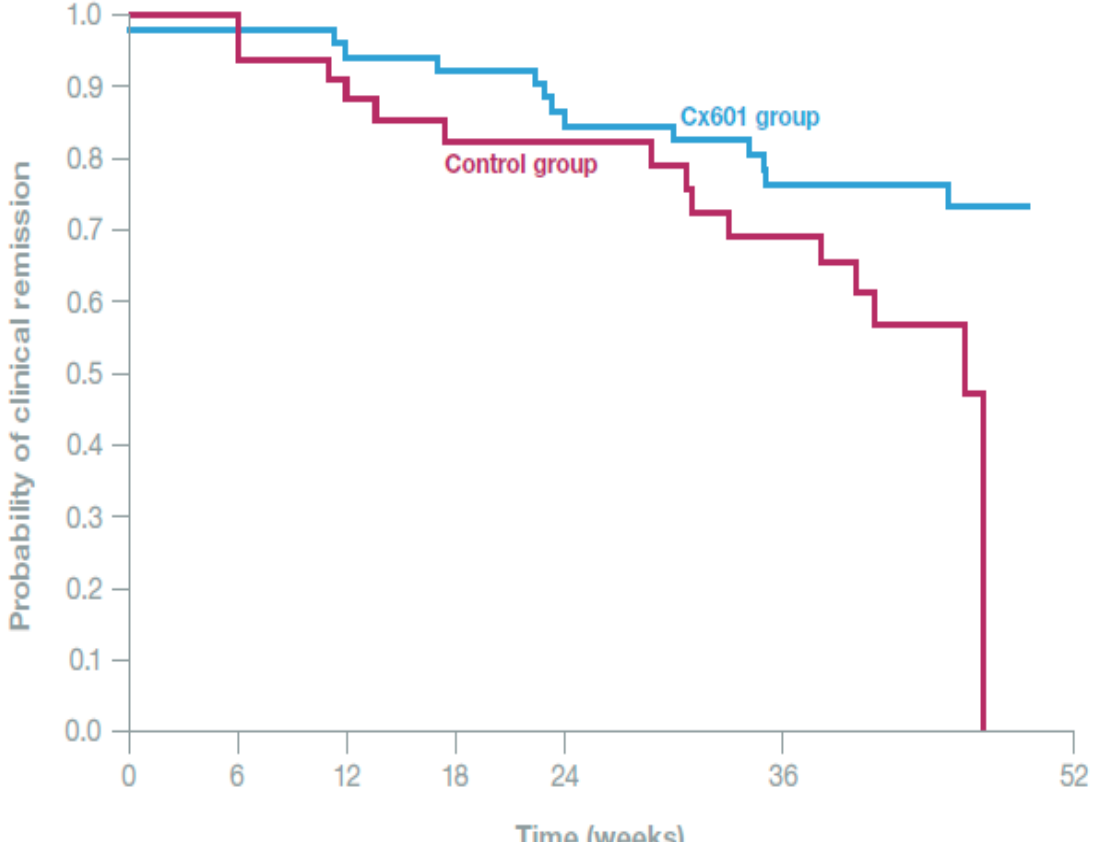
[2] Panés et al 2018

Time to clinical remission (A) and time to relapse (B) over a follow-up period of 52 weeks (ITT population, N=212)

(A) Time to clinical remission*

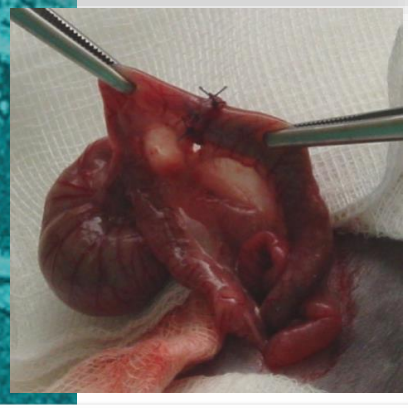


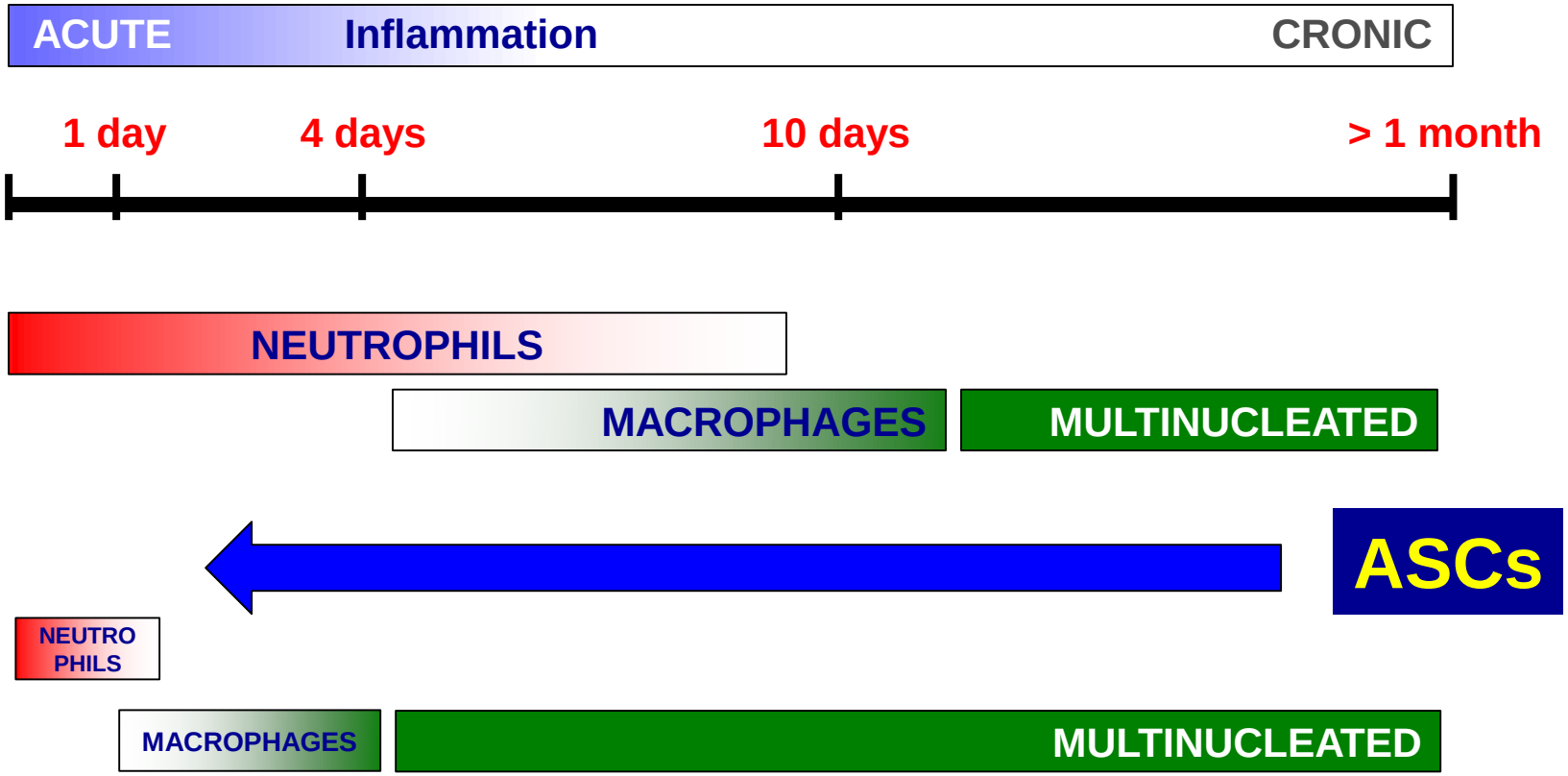
(B) Time to clinical relapse*



*Closure of all treated external openings.
ITT, intent-to-treat.
García-Olmo, D. *et al*. ECCO. Poster P691 (2018).

Speeding the healing!





European Journal of Cardio-Thoracic Surgery Advance Access published June 11, 2012
European Journal of Cardio-Thoracic Surgery 0 (2012) 1–8
doi:10.1093/ejcts/ezs357
ORIGINAL ARTICLE

Sutures enriched with adipose-derived stem cells decrease the local acute inflammation after tracheal anastomosis in a murine model†

Tihomir Georgiev-Hristov[a,b,*], Mariano García-Arranz[b,*], Ignacio García-Gómez[b], Miguel Angel García-Cabezas[c], Jacobo Trébol[b,b], Luz Vega-Clemente[b], Prudencio Díaz-Agero[d,§] and Damián García-Olmo[a,b,§]

Int J Colorectal Dis (2010) 25:1447–1451
DOI 10.1007/s00384-010-0952-3
ORIGINAL ARTICLE

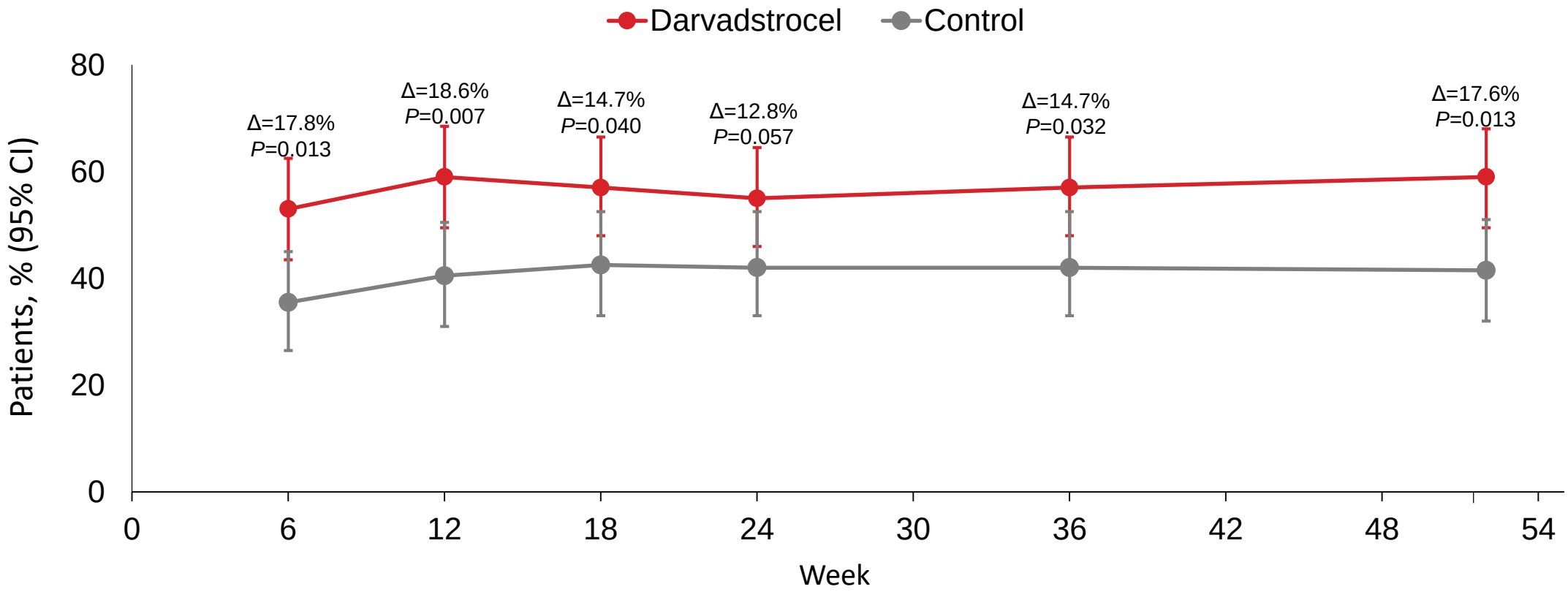
Biosutures improve healing of experimental weak colonic anastomoses

Isabel Pascual · Gemma Fernández de Miguel · Mariano García Arranz · Damián García-Olmo

Stem Cells superior to control in achieving clinical remission* at any time point up to week 52

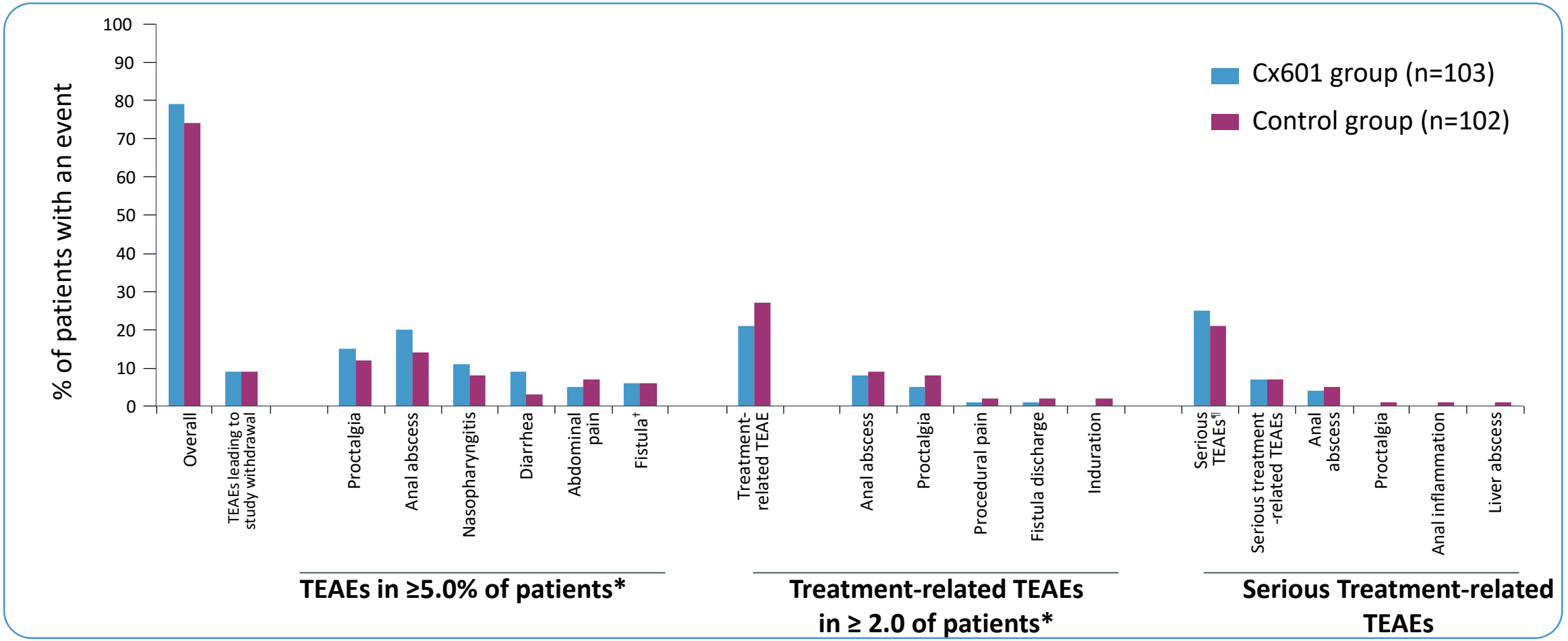
mITT population

- mITT, modified intention-to-treat.
  Panés J, et al. *Gastroenterology*. 2018;154(5):1334-1342.



*Closure of all treated external openings that were draining at baseline despite gentle finger compression.

Excellent Safety Profile to week 52 (Safety population, N=205)



*In either treatment group. †Includes the following preferred terms: anal abscess, anal fistula, fistula, fistula discharge and infected fistula. ¶Defined as any adverse event that at any dose resulted in death, was life-threatening, caused permanent incapacity or disability, resulted in hospital admission or prolonged a hospital stay, was a medically significant event, or was a suspected transmission of an infectious agent.
TEAE, treatment-emergent adverse event.
Panés, J. *et al*. Gastroenterology. 2018;154:133 4-1342.

What does it mean in real clinical terms?

The durable response that was observed with Cx601 over one-year suggests:

1. The need for major surgical interventions may be reduced: Less incontinence!
2. The need for systemic immunosuppression can be reduced: Less adverse events!
3. One year after a single administration in treatment-refractory Crohn's disease patients: Why not repeat doses?

THE LANCET

Articles

Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial

*Julián Panés, Damián García-Olmo, Gert Van Assche, Jean Frederic Colombel, Walter Reinisch, Daniel C Baumgart, Axel Dignass, Maria Nachury, Marc Ferrante, Lili Kazemi-Shirazi, Jean C Grimaud, Fernando de la Portilla, Eran Goldin, Marie Paule Richard, Anne Leselbaum, Silvio Danese, for the ADMIRE CD Study Group Collaborators**

Summary

Background Complex perianal fistulas in Crohn's disease are challenging to treat. Allogeneic, expanded, adipose-derived stem cells (Cx601) are a promising new therapeutic approach. We aimed to assess the safety and efficacy of Cx601 for treatment-refractory complex perianal fistulas in patients with Crohn's disease.

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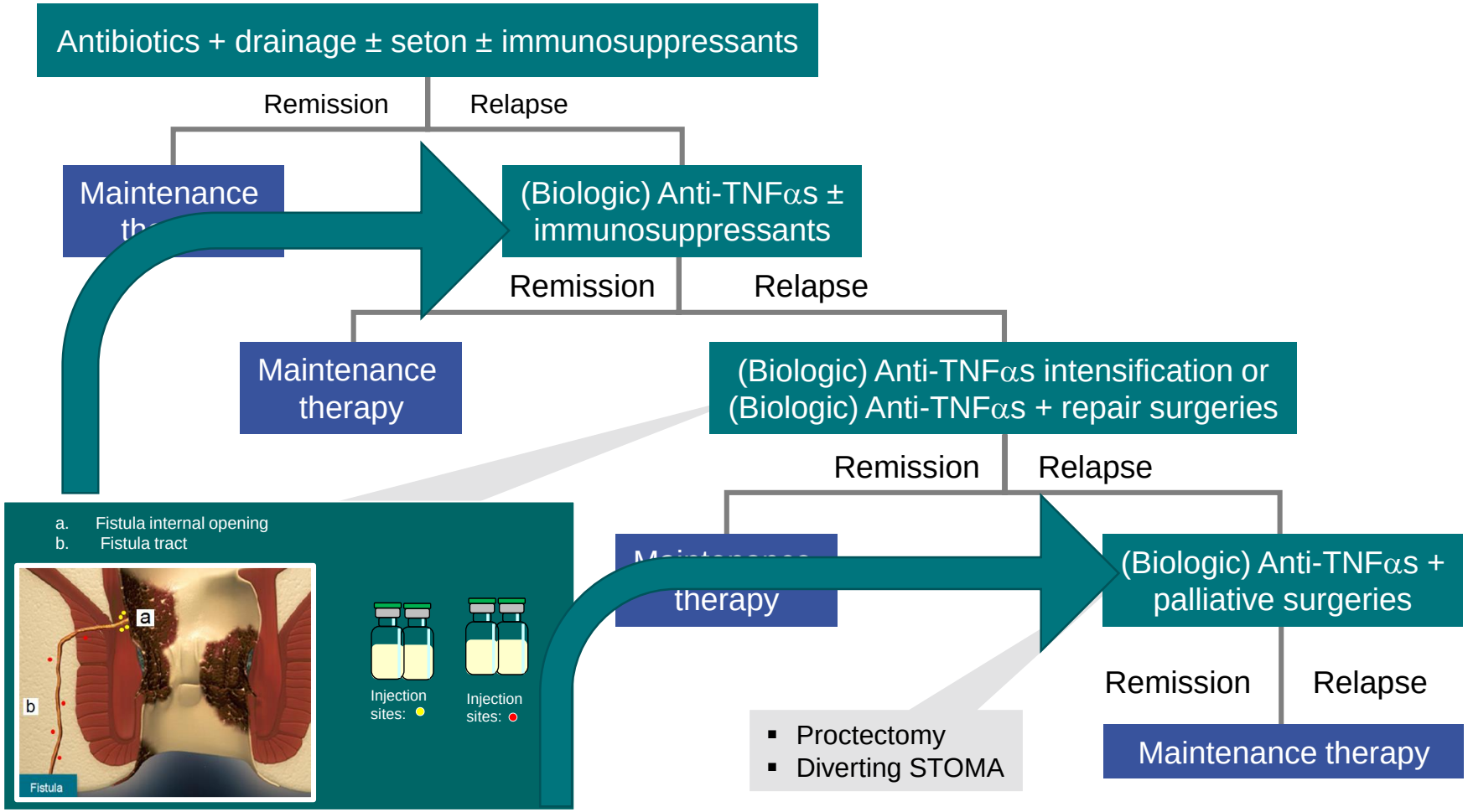
http://dx.doi.org/10.1016/S0140-6736(16)31203-X

Current technical options in CD anal fistulas

	RECURRENCE	INCONTINENCE	TECHNICAL DIFFICULTY	POSTOP PAIN
INTO FISTULA TRACTS • Fibrin glue , Plug • FilaC, VAAFT,…	+++	–	–	–
SETON	++	+	–	++/+
FLAPS	+	+	+++	++
SPHINCTEROPLASTY	+	+++	++	++
LIFT	+++	+	++	+
IDEAL TECHNIQUE	–	–	–	–
Darvadstrocel (Cx601)	+	–	–	–

The Revolution of Stem Cells



Adapted from Gecse KB, et al. *Gut*. 2014;63:1381-92;

CX601: DarVadstrocel

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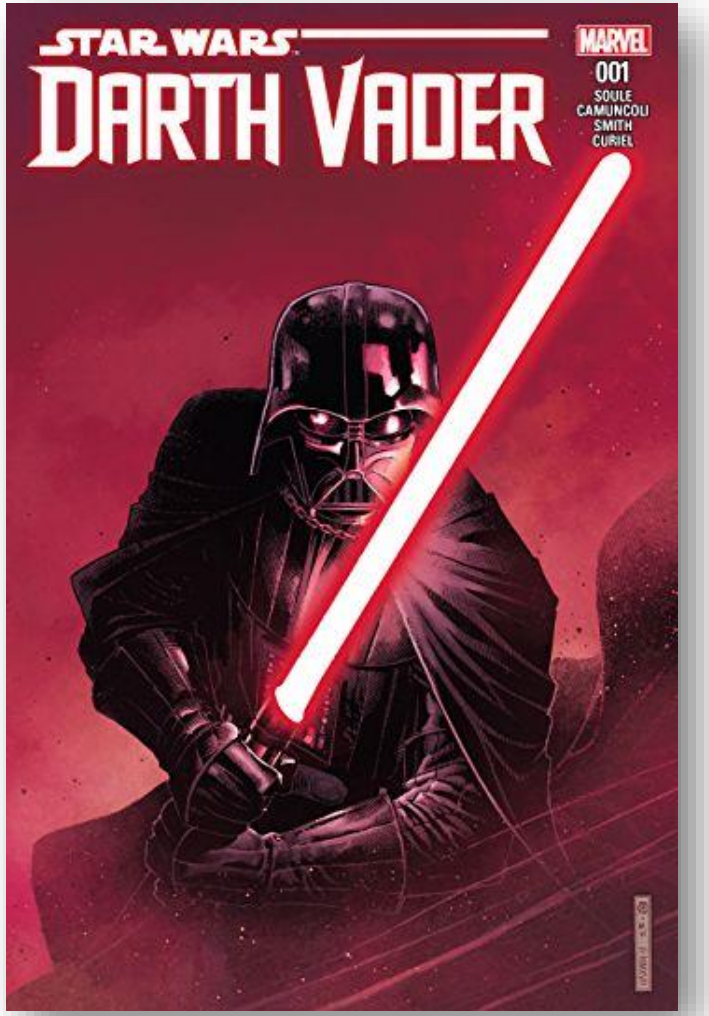

Thank you!