# TOP PAPERS FROM 2016:

# IBD & BIOSIMILARS

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CDDW, BANFF, AB

MARCH 5, 2017

UNIVERSITY OF CALGARY

Inflammatory Bowel Disease Group
University of Calgary

# FINANCIAL INTEREST DISCLOSURE (OVER THE PAST 24 MONTHS)

**Speaker: Janssen, Abbvie**

**Advisory boards: Janssen, Abbvie, Takeda, Shire, Allergan**

# BACKGROUND


**Increasing role of biologics in patient care**

**New products, new diseases**

**Growing share of overall drug spending**

**Forecast for Canada: $6.0 billion by 2020**

## Role of biologics

## Why is there a need for biosimilars?

**CT-P13 was the first mAb biosimilar approved in Canada (2014)**

# IBD TOP PAPERS FROM 2016


1. SYSTEMATIC REVIEW on BIOSIMILARS

2. CLINICAL TRIAL on BIOSIMILARS

# LEARNING OBJECTIVES

***At the end of this session participants should be able to***

- ***identify the differences between an originator monoclonal antibody and a biosimilar, and***
- ***to recognize the potential implications of switching from an originator product to a biosimilar.***

# CanMEDS Roles Covered

| | |
|---|---|
| X | **Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.) |
| X | **Communicator** (as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.) |
| X | **Collaborator** (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.) |
| X | **Leader** (as *Leaders*, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.) |
| X | **Health Advocate** (as *Health Advocates*, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.) |
| X | **Scholar** (as *Scholars*, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.) |
| X | **Professional** (as *Professionals,* physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.) |

# BACKGROUND – A PRIMER

**Biosimilars** aka as Subsequent Entry Biologics (SEBs)

**Biosimilars** are:
- NOT generic biologic molecules

- NOT identical to the reference biologics

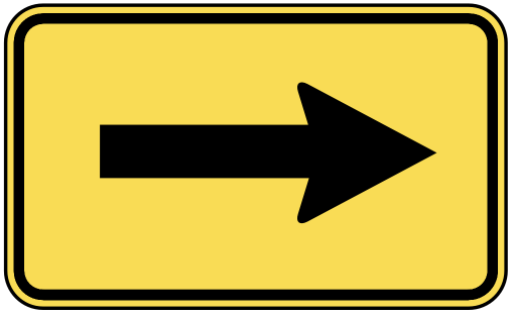

Health Canada, 2010. Guidance for sponsors: Information and submission requirements for subsequent entry biologics.
Available at: http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/seb-pbu/seb-pbu_2010-eng.php;

FDA Guidance for Industry. Biosimilarity, April 2015.
Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf

Kozlowski and Swann. Adv Drug Deliv Rev 2006;58:707–72; Dörner et al. Ann Rheum Dis 2013;72:322–8;

# PRIMER – REGULATORY PROCESS

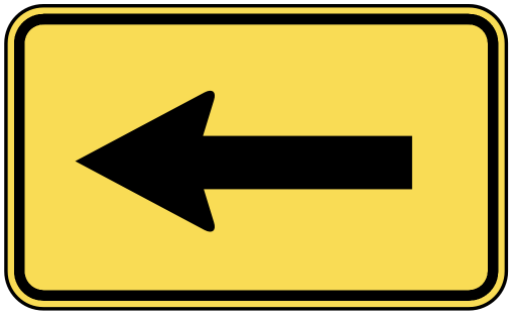
**The development of a <u>new molecule</u>**



# PRIMER – REGULATORY PROCESS

**Regulatory process for a biosimilar**

**Reverse of what is used for the development of a new molecule.**



# CDDW BIOSIMILAR SESSIONS

**Learning Theatre Sessions**

Sunday, March 5th 10:30 AM

**Hot Topics on Biosimilar infliximab – Takeaways from Most Recent Studies**

*Dr. Tore K. Kvien, Dep't of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway*

**CAG Symposium: IBD- Managing Biologics**

Monday, March 6th 8:00 AM

**Biosimilars: How do we make sure that we use them properly?**

*Niels Vande Casteele, University of California, San Diego*

# CHINGCUANCO ET AL.
## ANN INTERN MED. 2016 OCT 18;165(8):565-574.

Chingcuanco F, Segal JB, Kim SC, Alexander GC.

Bioequivalence of Biosimilar Tumor Necrosis Factor- Inhibitors Compared With Their Reference Biologics: A Systematic Review.

**Background: Biosimilars are of growing clinical, regulatory, and commercial importance.**

**Purpose: To summarize evidence about the bioequivalence between biosimilar and reference tumor necrosis factor(TNF) - inhibitors.**

# SYSTEMATIC REVIEW

**Data Sources:**

- PubMed
- EMBASE
- Cochrane Central Register of Controlled Trials
- LILACS
- ClinicalTrials.gov
- WHO International Clinical Trials Registry Platform
- EU Clinical Trials Register
- U.S. Food and Drug Administration
- European Medicines Agency

**From inception through <u>April 2016</u>**

# STUDY SELECTION

**Study Selection:**

Published full text only
English-language studies
Human studies
Any size or design

**Comparing a reference TNF-inhibitors with**

**Inclusion:**
Biosimilar TNF-inhibitors

**Exclusion:**
Biomimic TNF-inhibitors

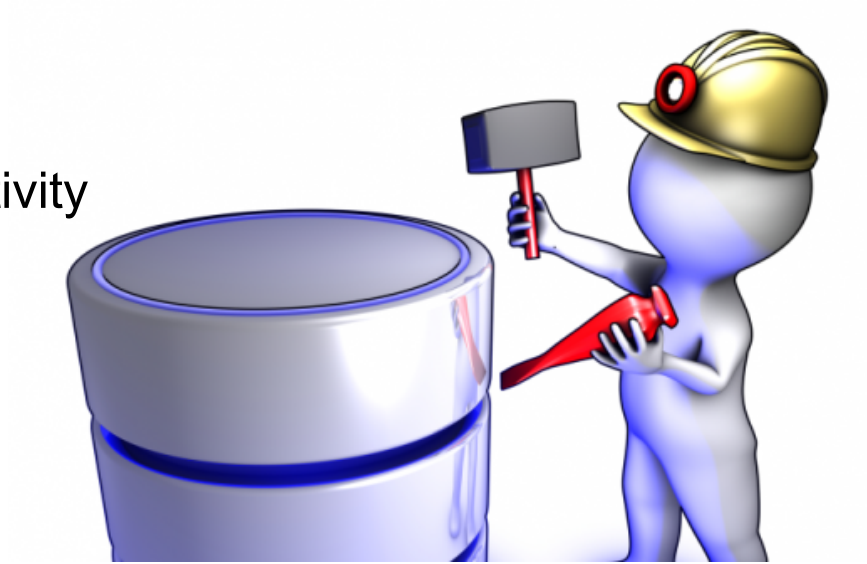
# DATA EXTRACTION

**Pharmacokinetic outcomes**
AUC, Cmax and Ctrough

**Clinical efficacy**
Standardized measures of disease activity

**Adverse events**

**Immunogenicity data**



# QUALITY ASSESSMENT


Cochrane Risk of Bias Tool
(for clinical trials)

Newcastle–Ottawa Scale
(for observational studies)

Detection bias

Attrition bias

Reporting bias

# ELIGIBLE STUDIES

| Type of study | # of studies | Types of participants |
|---|---|---|
| Phase 1 (safety) | 8 | Healthy volunteers (6)<br>AS (1), RA (1) |
| Phase 3 (effectiveness) | 5 | Rheumatoid arthritis (RA) |
| Observational | 6 | IBD (4) and RA (2) |

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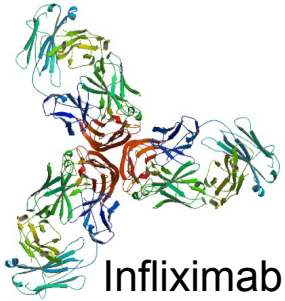
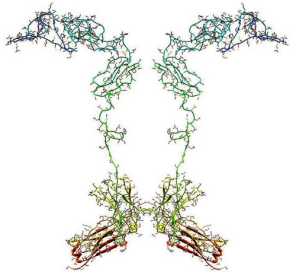
# STUDY DETAILS: PHASE 1 TRIALS

Biosimilar vs. reference biologic



Infliximab = 6



Etanercept = 2

Healthy volunteers (6), AS (1), RA (1)

Combination of open-label, single and double-blind, crossover and parallel-group trials.

Pharmacokinetic parameters

Satisfied pre-specified equivalence margin of 80% to 125%.

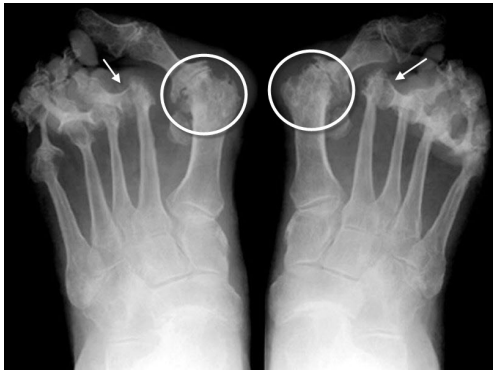
*Included PLANETAS. Not powered to assess clinical efficacy endpoints of ASAS20, ASAS40.*

# STUDY DETAILS: PHASE 3 TRIALS

5 parallel-group trials enrolling patients with RA *Included PLANETRA*

Sample size: 120-606 patients

Infliximab n=2, etanercept n=2, adalimumab n=1



Primary end point: ACR20 at 12-54 weeks

All phase 3 trials showed ‘equivalence’ *between biosimilars and reference biologics*

Similar adverse events - mild to moderate severity.

# STUDY DETAILS: OBSERVATIONAL

**All studies involved infliximab and CT-P13**

Cross-sectional studies (n=2; included 1 IBD study)
Cross-reactivity of antibodies (reference biologic, CT-P13)

Cohort studies (n=4; included 3 IBD studies)
CT-P13 at entry or one way switch (reference biologic to CT-P13)
Similar efficacy and safety outcomes
No comparator group
Heterogeneity of time of switch

# SUMMARY OF OUTCOMES

**Pharmacokinetic:**
‘Similar’ pharmacokinetic data … Equivalence margin of 80% to 125%

**Clinical:**
**‘**Similar’ clinical outcomes and safety data

**Safety:**
**‘**Similar’ rates of treatment-emergent adverse events (mild to moderate severity)
‘Similar’ rates of serious adverse events

**Immunological:**
10 of 13 trials assessed immunogenicity
Immunogenicity seemed comparable across treatment groups in all studies

# SUMMARY OF OUTCOMES

**No IBD patients in the listed clinical trials**

# CONCLUSION OF CHINGCUANCO STUDY

**Study's conclusion: Preliminary evidence supports the biosimilarity and interchangeability of biosimilar and reference TNF- inhibitors.**

**My take:**

- Comprehensive systematic review **to April 2016**
- Potential role of bias and lack of long term follow up
- Transition only (vs. switching)
- Heterogeneity in timing of 'switch'
- Insufficient controlled data to date on biosimilars in IBD
- Concerns about indication extrapolation

# IBD TOP PAPERS FROM 2016

Jørgensen K, Olsen I, Goll G et al.

**Biosimilar infliximab (CT-P13) is not inferior to originator infliximab: results from the 52-week randomized NOR-SWITCH trial.**

Latebreaker Oral Presentation. Abstract LB15. UEGW 2016.

Lancet 2017 (in press)

*A clinical trial that INCLUDES the IBD population*

# NOR-SWITCH TRIAL

Randomized (1:1), double-blind, parallel-group, phase IV study to evaluate the **safety and efficacy of switching from innovator infliximab to biosimilar infliximab** compared with continued treatment with innovator infliximab

ClinicalTrials.gov Identifier: NCT02148640

# NOR-SWITCH TRIAL


INTERVIEWER:
**DR. JOHN MARSHALL**
McMASTER UNIVERSITY

INTERVIEWEE:
**DR. BRIAN FEAGAN**
WESTERN UNIVERSITY

# NOR-SWITCH TRIAL

**Sponsor: Norway's Regional Health Authority**

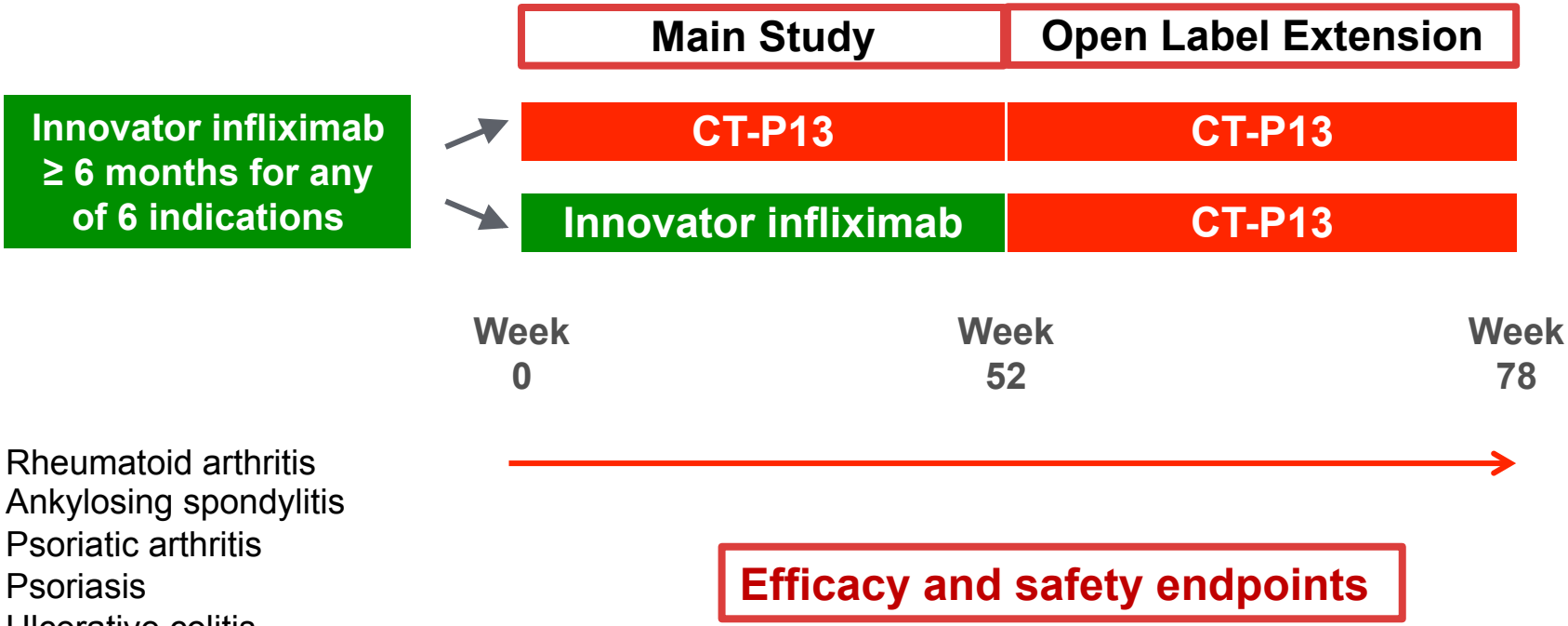
**Start date: Oct 2014**

***Primary study: Jul 2016 (week 52 clinical outcomes)***

***Secondary study: Jan 2017 (26 week extension i.e. to week 78)***

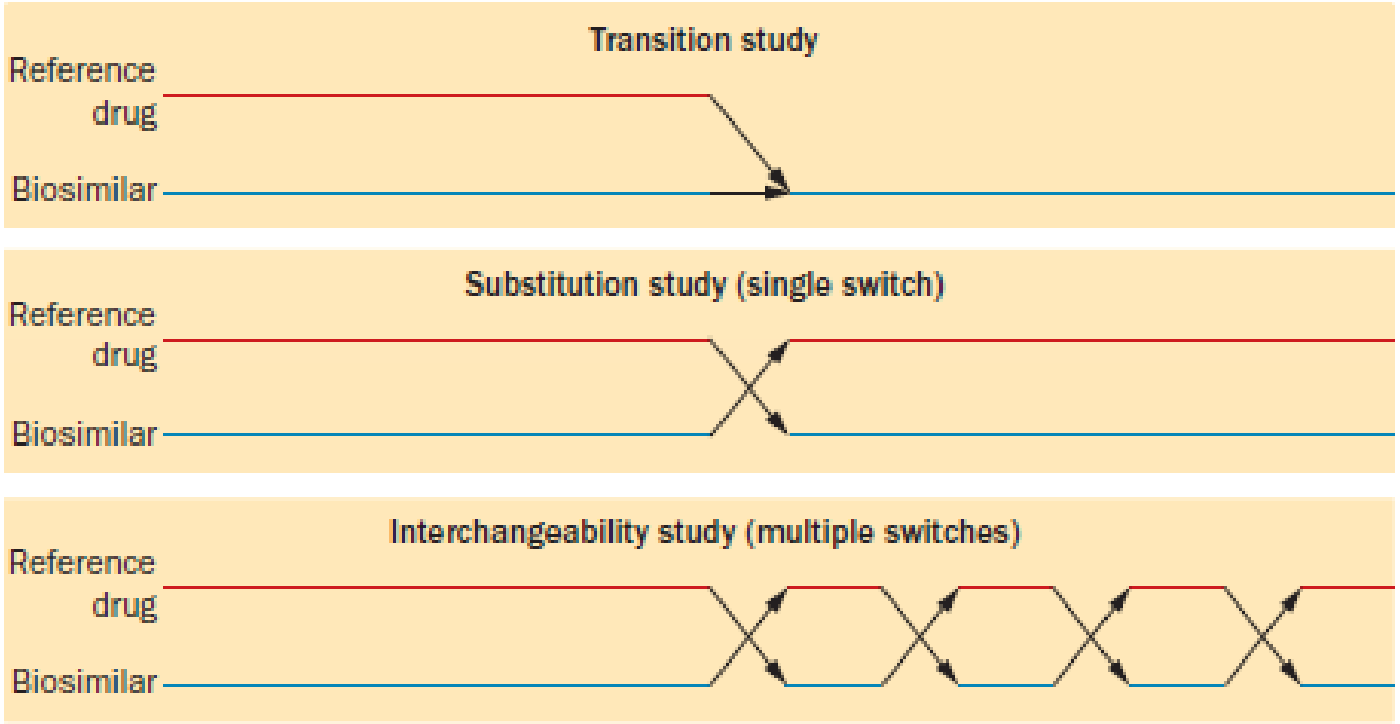
Adapted from https://clinicaltrials.gov/ct2/show/NCT02148640

# STUDY DESIGN




Jørgensen K, et al. UEGW 2016, Abstract LB15, NOR-SWITCH.

# ‘SWITCH’ STUDY DESIGNS




Dörner T, and Kay J. *Nat Rev Rheumatol.* 2015 Dec;11(12):713-24

# STUDY OBJECTIVES

**Primary**

To assess if CT-P13 is **non-inferior** to innovator infliximab with regard to disease worsening

**Secondary**

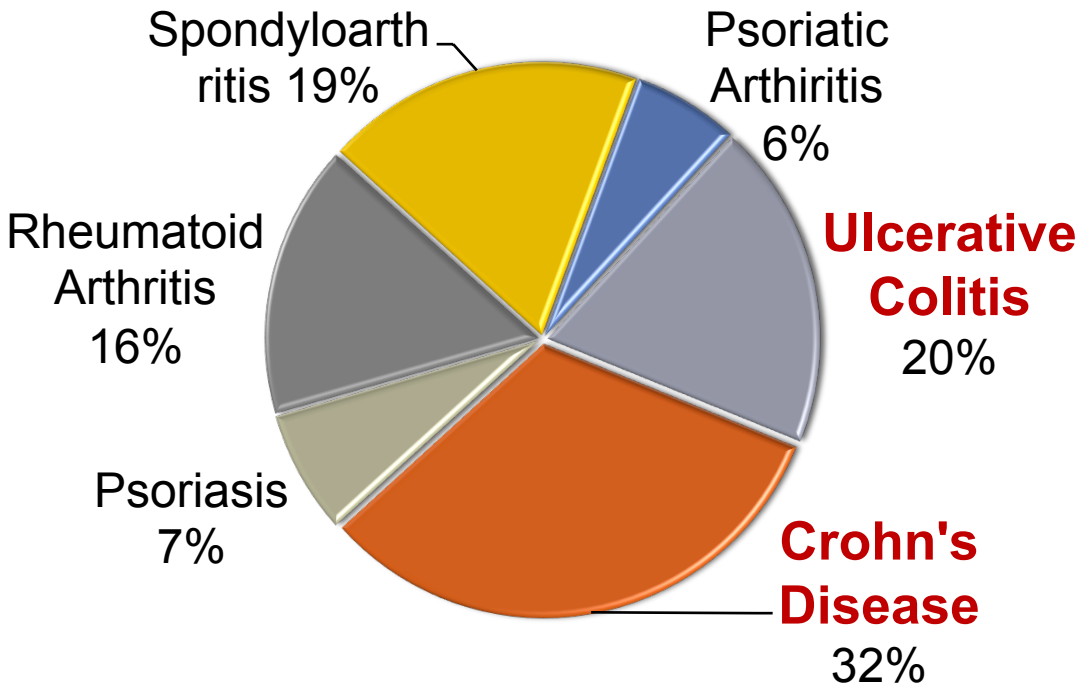
To assess the **safety and immunogenicity** of CT-P13 compared with innovator infliximab

To compare the **efficacy** of CT-P13 with innovator infliximab applying generic and disease-specific outcome measures

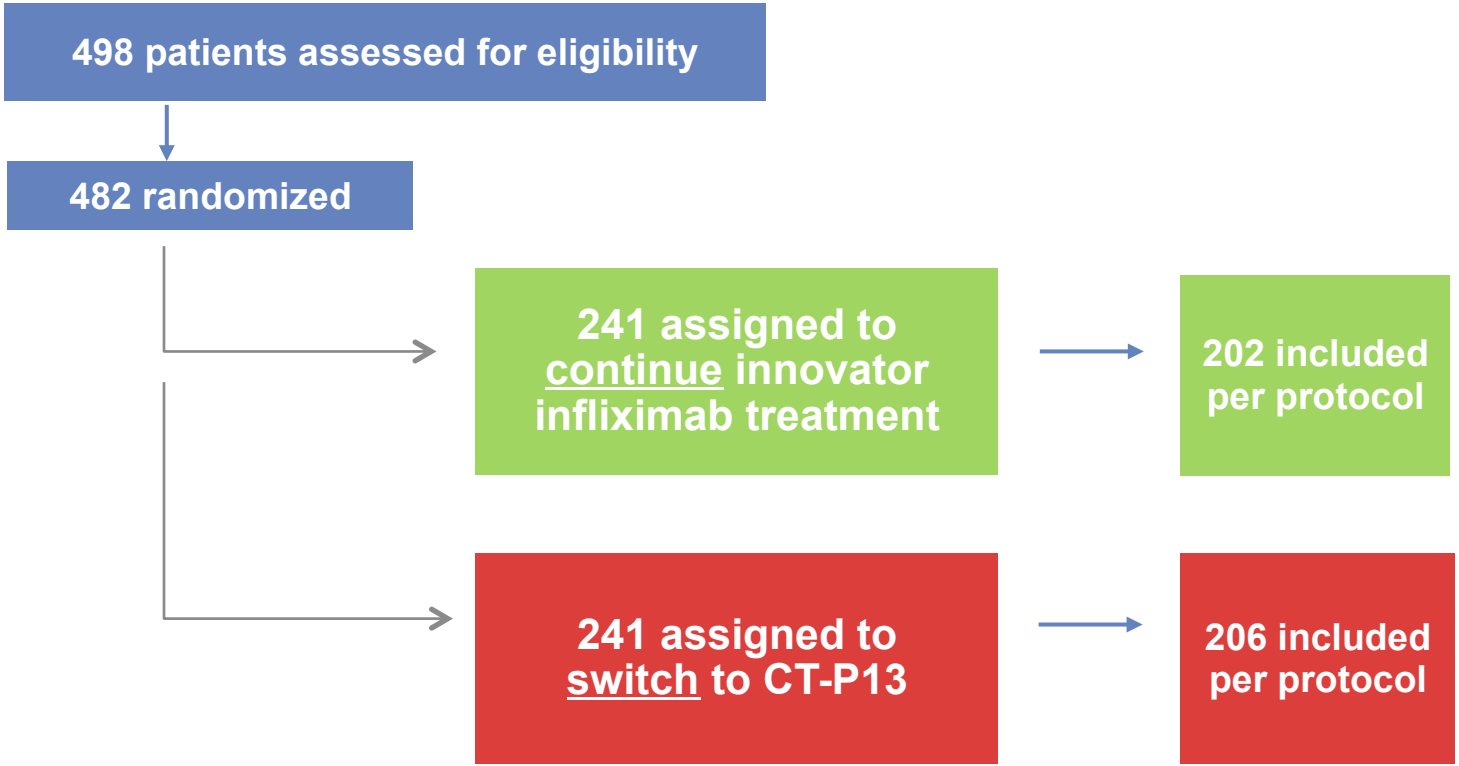
NB. All patients needed to have been on stable innovator infliximab treatment for ≥6 months

Jørgensen K, et al. UEGW 2016, Abstract LB15, Latebreaker Oral Presentation.

# NOR-SWITCH POPULATION (N=482)



# NOR-SWITCH STUDY FLOW




Jørgensen K, et al. UEGW 2016, Abstract LB15, Latebreaker Oral Presentation.

# BASELINE CHARACTERISTICS

| | Overall | | Crohn's Disease | | Ulcerative colitis | |
|---|---|---|---|---|---|---|
| | Innovator n=241 | CT-P13 n=240 | Innovator n=78 | CT-P13 n=77 | Innovator n=47 | CT-P13 n=46 |
| Age (yrs) | 47.5 (14.8) | 48.2 (14.9) | 38.0 (13.4) | 39.5 (14.2) | 45.8 (14.1) | 44.4 (14.8) |
| Disease duration (yrs) | 16.7 (10.9) | 17.5 (10.5) | 12.8 (9.0) | 14.3 (8.5) | 11.2 (9.2) | 11.5 (7.5) |
| Duration on innovator infliximab (yrs) | 6.7 (3.6) | 6.9 (3.8) | 5.7 (3.5) | 5.2 (3.3) | 4.2 (2.1) | 4.3 (2.5) |
| No previous biologic | 188 (78.0%) | 188 (78.3%) | 61 (78%) | 60 (78%) | 45 (96%) | 43 (93%) |
| One previous biologic | 43 (17.8%) | 40 (16.7%) | 17 (22%) | 17 (22%) | 2 (4%) | 2 (4%) |
| Concomitant immunosuppressant | 113 (46.9%) | 129 (53.8%) | 30 (38%) | 17 (22%) | 19 (40%) | 20 (43%) |

# BASELINE CHARACTERISTICS

| | Overall | | Crohn's Disease | | Ulcerative colitis | |
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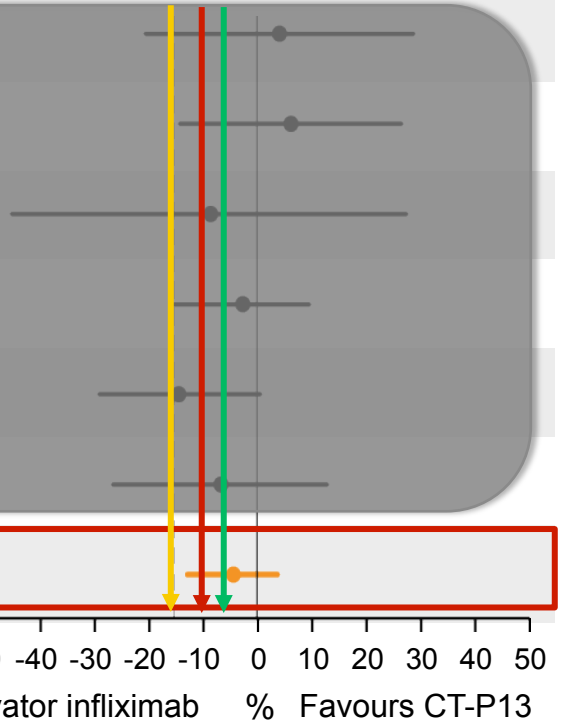
| Age (yrs) | 47.5 (14.8) | 48.2 (14.9) | **Younger** | | 45.8 (14.1) | 44.4 (14.8) |
| Disease duration (yrs) | 16.7 (10.9) | 17.5 (10.5) | **Shorter disease duration** | | | |
| Duration on innovator infliximab (yrs) | 6.7 (3.6) | 6.9 (3.8) | **Shorter exposure to innovator infliximab** | | | |
| No previous biologic | 188 (78.0%) | 188 (78.3%) | 61 (78%) | 60 (78%) | **More bio-naive** | |
| One previous biologic | 43 (17.8%) | 40 (16.7%) | **More bio-exposed** | | 2 (4%) | 2 (4%) |
| Concomitant immunosuppressant | **More likely to be on concomitant therapy** | | 30 (38%) | 17 (22%) | 19 (40%) | 20 (43%) |

# PRIMARY ENDPOINT: DISEASE WORSENING

| Diagnosis | Innovator infliximab (n=202) | CT-P13 (n=206) | Adjusted Rate Difference (95% CI) |
|---|---|---|---|
| Rheumatoid arthritis | 11 (36.7%) | 9 (30.0%) | 4.5% (-20.3 - 29.3%) |
| Spondyloarthritis | 17 (39.5%) | 14 (33.3%) | 6.3% (-14.5 - 27.2%) |
| Psoriatic arthritis | 7 (53.8%) | 8 (61.5%) | -8.7% (-45.5 - 28.1%) |
| Ulcerative colitis | 3 (9.1%) | 5 (11.9%) | -2.6% (-15.2 - 10.0%) |
| Crohn's disease | 14 (21.2%) | 23 (36.5%) | -14.3% (-29.3 - 0.7%) |
| Psoriasis | 1 (5.9%) | 2 (12.5%) | -6.7% (-26.7 - 13.2%) |
| **Overall** | **53 (26.2%)** | **61 (29.6%)** | **-4.4% (-12.7 - 3.9%)** |




Jørgensen K, et al. UEGW 2016, Abstract LB15, Latebreaker Oral Presentation.

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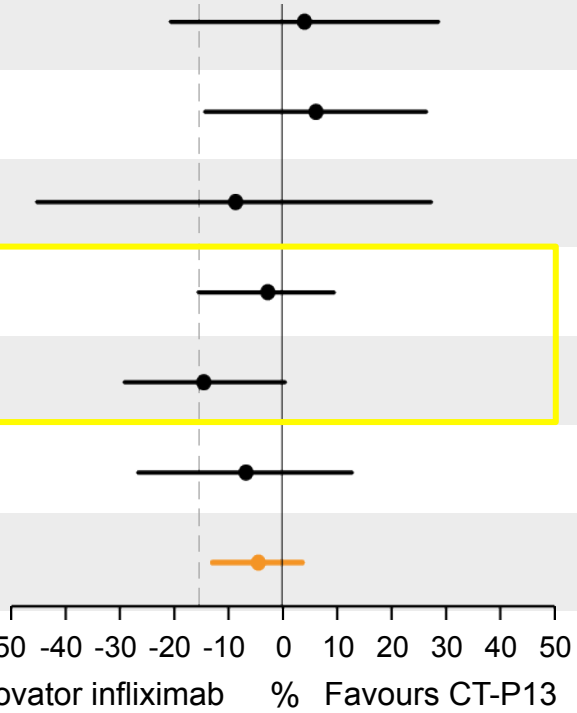


Jørgensen K, et al. UEGW 2016, Abstract LB15, Latebreaker Oral Presentation.

# ADVERSE EVENTS

| Type of event | Innovator infliximab (n=241) | CT-P13 (n=240) |
|---|---|---|
| Serious adverse events | 24 (10.0%) | 21 (8.8%) |
| Adverse events | 168 (69.7%) | 164 (68.3%) |
| Withdrawal due to adverse events | 9 (3.7%) | 8 (3.3%) |

Jørgensen K, et al. UEGW 2016, Abstract LB15, Latebreaker Oral Presentation.

# CONCLUSION

NOR-SWITCH suggests that a switch from innovator infliximab to biosimilar infliximab was not inferior to continued treatment with the innovator in patients with stable chronic disease.

*My take:*

*First RCT on biosimilars in the IBD population*

Jørgensen K, et al. UEGW 2016, Abstract LB15, Latebreaker Oral Presentation.

# STRENGTHS

**Innovative**

**Randomized controlled trial**

**First to include IBD patients**

**Government financed**

**No industry involvement**

Jørgensen K, et al. UEGW 2016, Abstract LB15, Latebreaker Oral Presentation.

# CONSIDERATIONS

1. Is NOR-SWITCH a true **switching study**?

*A one-way transition study*

2. Is the study **powered** to draw conclusions?

*Powered for the total sample size across indications*

3. Is there **valid assessment of disease worsening**?

*Objective and subjective criteria*

4. What are the **long-term outcomes**?

# WATCH THIS SPACE


**Full publication of NOR-SWITCH**

**Week 78 open label extension data from NOR-SWITCH**

**Phase III trial of CT-P13 in Crohn's disease**
*A Randomized, Double-Blind, Parallel-Group, Phase 3 Study to Demonstrate Noninferiority in Efficacy and to Assess Safety of CT-P13 Compared to Remicade in Patients With Active Crohn's Disease (n=220)*
**ClinicalTrials.gov Identifier:**NCT02096861

- 4 arms; innovator infliximab, biosimilar, innovator switch, biosimilar switch
- All participants are biologic naive

# Evaluation and Certificate of Attendance

**Please download the CDDW™ app to complete the session evaluation and to receive your certificate of attendance.**