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Effectiveness and Safety of Reference Infliximab and Biosimilar in Crohn Disease: A French Equivalence Study

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Background: CT-P13 is a biosimilar of the reference product (RP) infliximab, with demonstrated efficacy and safety for some inflammatory arthritides. It was approved for the treatment of Crohn disease (CD) on that basis, without specific studies examining its effects in CD.

Objective: To compare the effectiveness and safety of CT-P13 and RP in infliximab-naive patients with CD.

Design: Comparative equivalence cohort study.

Setting: Système National des Données de Santé (SNDS), a French nationwide health administrative database (1 March 2015 to 30 June 2017).

Patients: 5050 infliximab-naive patients with CD who were older than 15 years, had started treatment with RP (n = 2551) or CT-P13 (n = 2499), and had no other indications for infliximab.

Measurements: The primary outcome was a composite end point of death, CD-related surgery, all-cause hospitalization, and reimbursement of another biologic therapy. Equivalence was defined as a 95% CI of the hazard ratio (HR) of CT-P13 versus RP in a multivariable marginal Cox model situated within prespecified margins (0.80 to 1.25).

Results: Overall, 1147 patients in the RP group and 952 patients in the CT-P13 group met the composite end point (including 838 and 719 hospitalizations, respectively). In multivariable analysis of the primary outcome, CT-P13 was equivalent to RP (HR, 0.92 [95% CI, 0.85 to 0.99]). No differences in safety outcomes were observed between the 2 groups: serious infections (HR, 0.82 [CI, 0.61 to 1.11]), tuberculosis (HR, 1.10 [CI, 0.36 to 3.34]), and solid or hematologic cancer (HR, 0.66 [CI, 0.33 to 1.32]).

Limitation: The SNDS does not contain all relevant clinical data (for example, disease activity).

Conclusion: This analysis of real-world data indicates that the effectiveness of CT-P13 is equivalent to that of RP for infliximab-naive patients with CD. No difference was observed for safety outcomes.

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Infliximab is an anti–tumor necrosis factor (TNF) monoclonal antibody approved for the treatment of Crohn disease (CD), ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, and chronic plaque psoriasis. The TNF inhibitors, including infliximab, have improved the management of inflammatory bowel disease (1). The U.S. Food and Drug Administration defines biosimilars as "highly similar to the reference product (RP) notwithstanding minor differences in clinically inactive components and for which there are no clinically meaningful differences between the biologic product and the reference product in terms of safety, purity, and potency of the product" (2). The patent for the RP infliximab (Remicade [Janssen Biotech, Horsham, Pennsylvania]) expired in 2015 in Europe. Biosimilar infliximab CT-P13 was approved by the European Medicines Agency in 2013.

The phase 1 PLANETAS study (3) and the phase 3 PLANETRA study (4) were conducted in infliximab-naive patients with ankylosing spondylitis and rheumatoid arthritis, respectively. CT-P13 has been approved for the treatment of these two diseases, and this approval has been extended to other diseases, including CD. The principle of extrapolation remains controversial (5, 6) because of minor structural differences between CT-P13 and RP and because of the possible differences in the mechanisms of action of infliximab across indications (7). The NOR-SWITCH randomized noninferiority trial (8) included 129 patients in the CD subgroup. Disease worsened more frequently in patients who switched to CT-P13 than in those who continued use of the RP (14.3%) and almost reached the prespecified noninferiority margin (15%). A 6-week randomized trial conducted in 220 patients with CD showed no difference between CT-P13 and RP in efficacy and safety (9). Other published prospective studies of CT-P13 have provided reassuring results but did not directly compare CT-P13 and RP (10–15). In view of these results, larger and longer-term studies are needed.

The study hypothesis was that CT-P13 and RP are equivalent. The European Medicines Agency and the U.S. Food and Drug Administration recommend equivalence trials to demonstrate biosimilarity (2, 16). Randomized controlled trials conducted with CT-P13 in rheumatoid arthritis and spondyloarthritis were equivalence trials (PLANETAS and PLANETRA [3, 4]); this is also the case for adalimumab (17). We aimed to compare the effectiveness and safety of CT-P13 and RP in a large nationwide observational equivalence cohort study of infliximab-naive patients with CD.

See also:

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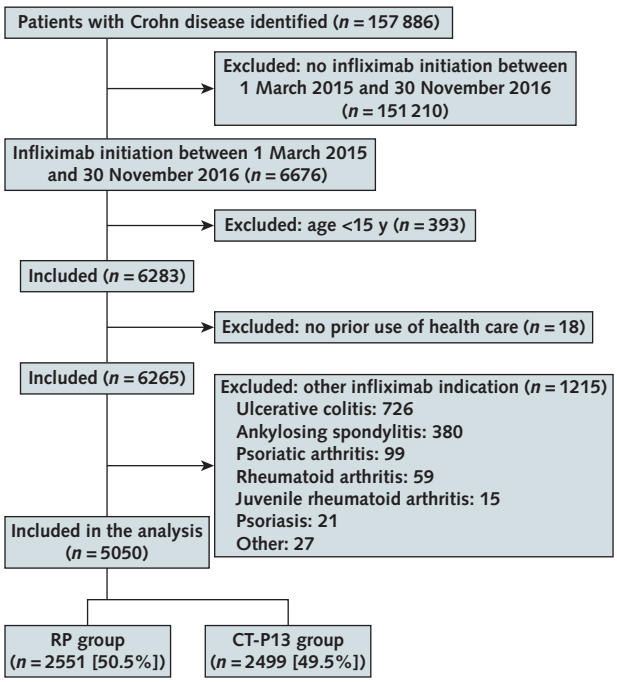
Figure 1. Study flow diagram.



Patients may have had more than 1 infliximab indication.
RP = reference product.

METHODS

Data Source

This study was conducted using the Système National des Données de Santé (SNDS) French nationwide health administrative database (18). This database covers more than 99% of the French population (around 65 million people). Each person is identified by a unique, anonymous number. The SNDS contains all outpatient (drugs, imaging, or endoscopic investigations) and inpatient information (diagnoses; procedures performed; and expensive drugs dispensed, including anti-TNF agents). Patients with long-term diseases (LTDs), such as CD, are reimbursed for their health expenditure, and their diagnosis is recorded. The SNDS also contains sociodemographic data and, when applicable, the date of death. Details are given in the Appendix (available at Annals.org).

Study Population

This study was designed as a real-life comparative equivalence cohort study. All patients diagnosed with CD before 31 December 2016 were identified in the SNDS. An individual was considered to have been diagnosed with CD when he or she was eligible as having an LTD (since 1 January 2006) or had a hospital discharge diagnosis of CD (since 1 January 2010) (19) (Appendix Table 1, available at Annals.org). Infliximab-naive patients with CD who received at least 1 infliximab infusion between 1 March 2015 and 30 November 2016 were included. An infliximab-naive patient was defined as a patient who had not been reimbursed for infliximab during the previous 12 months. A diagnosis of CD had to be reported within 30 days after initiation of infliximab, to take into account longer hospital stays or administrative delays related to LTD procedures.

Patients younger than 15 years were excluded owing to the very small number of CT-P13 dispensings. Patients who did not receive outpatient health care during the 3 years before initiating infliximab therapy were excluded. These patients may have lived outside of France or may not have any outpatient data entered in the SNDS (<1% of the French population). Patients who received anti-TNF for diagnoses other than CD before the first infliximab infusion were also excluded (Appendix Table 1). Patients with a diagnosis of cancer during the previous 5 years were excluded from analysis of the secondary outcome of cancer.

Exposure Definition

The primary exposures of interest were infliximab: CT-P13 or RP. The other infliximab biosimilar, SB2, was not studied, because it has been marketed in France only since 2017. In France, infliximab is administered in either public or private hospitals. When the first infliximab reimbursement corresponded to the RP, the patient was included in the RP group, and when the first infliximab reimbursement corresponded to CT-P13, the patient was included in the CT-P13 group. Follow-up started 30 days after the first infusion. Patients were followed until onset of a predefined outcome or censoring. Patients were censored at study end (30 June 2017), switch from RP to CT-P13 (or vice versa) plus 30 days, or discontinuation of infliximab. In the secondary outcome cancer analysis, patients were censored at study end (30 June 2017) or switch from RP to CT-P13 (or vice versa) plus 30 days. Discontinuation of infliximab was defined as the absence of drug dispensing for 56 days (theoretical coverage) + 60 days = 116 days.

Outcomes

The primary outcome was a composite end point of death; CD-related surgery; all-cause hospitalization except childbirth (Appendix Table 1) for at least 1 night; or reimbursement of adalimumab, vedolizumab, or ustekinumab. Only the first event was considered. Crohn disease–related surgery included bowel resection, stricturoplasty, new intestinal stoma, and surgery for anorectal abscess or fistula (Appendix Table 2, available at Annals.org). Because adalimumab, vedolizumab, and ustekinumab are not coadministered with infliximab, use of these biologic therapies indicates failure or toxicity of infliximab therapy. This primary outcome assessed effectiveness because it includes all-cause hospitalization.

Secondary outcomes were CD-related hospitalization, CD-related surgery except for anorectal abscess or fistula surgery, or each individual item of the composite end point. Serious infection (defined as infection requiring hospitalization), except for intestinal or anorectal abscess or fistula (20), tuberculosis (21), and solid or hematologic cancer (22), were also assessed (Appendix Table 1).

Table 1. Demographic and Baseline Patient Characteristics*

Characteristic	All Patients (*n* = 5050), *n* (%)	RP Group (*n* = 2551), *n* (%)	CT-P13 Group (*n* = 2499), *n* (%)
Sex			
Male	2344 (46.4)	1171 (45.9)	1173 (46.9)
Female	2706 (53.6)	1380 (54.1)	1326 (53.1)
Age			
15–24 y	1268 (25.1)	683 (26.8)	585 (23.4)
25–34 y	1412 (28.0)	717 (28.1)	695 (27.8)
35–44 y	953 (18.9)	486 (19.1)	467 (18.7)
45–54 y	685 (13.6)	315 (12.3)	370 (14.8)
≥55 y	732 (14.5)	350 (13.7)	382 (15.3)
CD duration†			
<6 mo	1374 (27.2)	650 (25.5)	724 (29.0)
6 mo–1 y	1028 (20.4)	528 (20.7)	500 (20.0)
2–6 y	1148 (22.7)	581 (22.8)	567 (22.7)
>6 y	1500 (29.7)	792 (31.0)	708 (28.3)
CD site			
Colon	721 (14.3)	368 (14.4)	353 (14.1)
Small bowel	1196 (23.7)	590 (23.1)	606 (24.2)
Colon and small bowel	1274 (25.2)	649 (25.4)	625 (25.0)
Unspecified	1859 (36.8)	944 (37.0)	915 (36.6)
Complementary universal health insurance status	735 (14.6)	365 (14.3)	370 (14.8)
Deprivation index			
Missing	161 (3.2)	114 (4.5)	47 (1.9)
Quintile 1 (less deprived)	788 (15.6)	377 (14.8)	411 (16.4)
Quintile 2	869 (17.2)	438 (17.2)	431 (17.2)
Quintile 3	971 (19.2)	491 (19.2)	480 (19.2)
Quintile 4	1023 (20.3)	498 (19.5)	525 (21.0)
Quintile 5 (more deprived)	1238 (24.5)	633 (24.8)	605 (24.2)
Procedures			
Colonoscopy‡	3592 (71.1)	1791 (70.2)	1801 (72.1)
Gastroscopy‡	2176 (43.1)	1076 (42.2)	1100 (44.0)
Capsule endoscopy‡	163 (3.2)	82 (3.2)	81 (3.2)
Abdominal or pelvic CT‡	2286 (45.3)	1085 (42.5)	1201 (48.1)
Abdominal or pelvic MRI‡	2375 (47.0)	1110 (43.5)	1265 (50.6)
Anal ultrasonography‡	18 (0.4)	12 (0.5)	6 (0.2)
Drug exposures			
Aminosalicylates‡	1656 (32.8)	880 (34.5)	776 (31.1)
Budesonide‡	1164 (23.0)	571 (22.4)	593 (23.7)
Corticosteroids§			
0	2050 (40.6)	1031 (40.4)	1019 (40.8)
<1 g	759 (15.0)	407 (16.0)	352 (14.1)
1–2 g	762 (15.1)	351 (13.8)	411 (16.4)
2–3 g	494 (9.8)	243 (9.5)	251 (10.0)
>3 g	985 (19.5)	519 (20.3)	466 (18.6)
Thiopurine			
None	2347 (46.5)	1230 (48.2)	1117 (44.7)
Prior	662 (13.1)	352 (13.8)	310 (12.4)
Combination therapy	1076 (21.3)	456 (17.9)	620 (24.8)
Prior and combination therapy	965 (19.1)	513 (20.1)	452 (18.1)
Methotrexate‡	291 (5.8)	149 (5.8)	142 (5.7)
Last biologic therapy‡			
None	3604 (71.4)	1827 (71.6)	1777 (71.1)
Adalimumab	1374 (27.2)	678 (26.6)	696 (27.9)
Vedolizumab	59 (1.2)	36 (1.4)	23 (0.9)
Ustekinumab	13 (0.3)	10 (0.4)	3 (0.1)
Duration of all-cause hospitalization‡‖	0		
0 nights	2254 (44.6)	1189 (46.6)	1065 (42.6)
<3 nights	702 (13.9)	367 (14.4)	335 (13.4)
3 nights to 1 wk	699 (13.8)	358 (14.0)	341 (13.6)
1–2 wk	670 (13.3)	314 (12.3)	356 (14.2)
>2 wk	725 (14.4)	323 (12.7)	402 (16.1)

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Table 1–Continued

Characteristic	All Patients (*n* = 5050), *n* (%)	RP Group (*n* = 2551), *n* (%)	CT-P13 Group (*n* = 2499), *n* (%)
Duration of CD-related hospitalization‡‖	0		
0 nights	2631 (52.1)	1400 (54.9)	1231 (49.3)
<3 nights	613 (12.1)	313 (12.3)	300 (12.0)
3 nights to 1 wk	608 (12.0)	297 (11.6)	311 (12.4)
1–2 wk	622 (12.3)	292 (11.4)	330 (13.2)
>2 wk	576 (11.4)	249 (9.8)	327 (13.1)
Surgery‡			
Colon/small-bowel surgery	296 (5.9)	137 (5.4)	159 (6.4)
Anorectal abscess or fistula surgery	521 (10.3)	239 (9.4)	282 (11.3)
Year of infliximab initiation			
2015	2375 (47.0)	1667 (65.3)	708 (28.3)
2016	2675 (53.0)	884 (34.7)	1791 (71.7)
Hospital			
General	1771 (35.1)	900 (35.3)	871 (34.9)
University	1876 (37.1)	787 (30.9)	1089 (43.6)
Private	1403 (27.8)	864 (33.9)	539 (21.6)

CD = Crohn disease; CT = computed tomography; MRI = magnetic resonance imaging; RP = reference product.
* Percentages may not sum to 100 owing to rounding.
† Time from first diagnosis.
‡ At least once during the 12 mo before cohort entry.
§ Cumulative prednisone equivalent corticosteroid dose during the 12 mo before cohort entry.
‖ Without CD-related surgery.

Covariates

Covariates were time-fixed at cohort entry and included sociodemographic data: sex, age, complementary universal health insurance status (free access to health care for people with low income), and a deprivation index expressed in quintiles that was developed in France as the first component of a principal component analysis of 4 socioeconomic variables (23).

The interval since CD-related LTD or hospitalization was used as a proxy for CD duration. The CD site was identified by the fourth character of the International Classification of Diseases, 10th Revision (ICD-10), code: small bowel, colon, both, or unspecified. Proxies for CD severity were defined during the 12 months before initiation of infliximab and consisted of abdominal or pelvic computed tomography or magnetic resonance imaging, anal ultrasonography, gastroscopy, colonoscopy, or capsule endoscopy; cumulative duration of CD-related overnight hospitalizations (excluding CD-related surgery); CD-related surgery (**Appendix Table 2**); and exposure to aminosalicylates, corticosteroids (cumulative prednisone equivalent dose), budesonide, thiopurines (azathioprine, 6-mercaptopurine), methotrexate, or another biologic therapy. Crohn disease–related surgery included colon /small-bowel surgery and anorectal abscess or fistula surgery. Prior thiopurine exposure was defined as dispensing of thiopurine during the 12 months before infliximab initiation except for the last month. Thiopurine combination therapy was defined as thiopurine dispensing between 1 month before and 1 month after infliximab initiation. The last exposure to other biologic therapies was based on dispensing of adalimumab, vedolizumab, and ustekinumab, because these drugs are usually used in this order.

Cumulative duration of all-cause overnight hospitalizations without CD-related surgery was used as a proxy for general health condition during the 12 months before cohort entry. The type of hospital (university, general, or private) in which the first infliximab infusion was administered was also taken into account.

Statistical Analysis

Sample size was determined according to the formula proposed by Chow and colleagues (24), based on the therapeutic equivalence of CT-P13 and RP and an expected event rate of 40% in each group (25). A sample of 2173 patients was required for a 2-sided α level of 0.05, a power of 90%, and a 2-sided equivalence margin of 0.80 to 1.25.

In an equivalence trial, 2 treatments can be considered equivalent when the treatment hazard ratio (HR) and CI are situated within the predefined clinical equivalence margins: [Δ − 1/Δ]. Equivalence margins in biosimilar arthritis trials were an absolute difference of 15%, and the noninferiority margin in NOR-SWITCH was also 15% (4, 8, 26, 27). Equivalence margins of 10% were used in our study, because such margins can be considered to be more clinically relevant. These 10% margins correspond to relative margins of 0.80 to 1.25. The more stringent 95% CI recommended by the European Medicines Agency (28) was used (90% CI for the U.S. Food and Drug Administration [29]).

Descriptive analysis of covariates at cohort entry was performed: median and interquartile range (IQR) for continuous variables, and proportions for dichotomous and class variables. Comparative survival analysis between CT-P13 and RP was then performed: cumula-

tive incidence plot, log-rank test, and marginal Cox proportional hazards regression model to estimate adjusted HRs and their 95% CIs. The marginal Cox model is a population average model used for clustered events (30). In this case, the cluster is the hospital, because the choice between CT-P13 or RP is rarely decided by the clinician but instead corresponds to the hospital pharmacy's choice for all hospital patients. This model was used for the primary and secondary outcomes. Details are given in the **Appendix**.

Although the primary outcome corresponded to a 2-sided equivalence study, 2-sided superiority analysis with an α level of 0.05 was performed to test secondary outcomes. If the primary outcome was in favor of the equivalence of CT-P13 and RP, the composite end point was analyzed for heterogeneity according to sex, age, CD duration, CD type, and exposure to thiopurines by an interaction test.

Because the choice of the follow-up start date (day of first infliximab infusion + 30 days) and end date (56 days + 60 days) was in part arbitrary, various sensitivity analyses were conducted using alternative follow-up start dates (day of first infliximab infusion) and end dates (56 days + 30 days, or 56 days + 90 days). Other sensitivity analyses used the primary outcome analysis without a marginal model, or excluding patients who received infliximab between 1 January 2009 and 12 months before initiation of infliximab, or with the inverse probability of treatment weighting method (31–34). Details are provided in the **Appendix**.

We also calculated the E-value, which is the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the treatment and the outcome, conditional on the measured covariates, to explain away a treatment–outcome association (35).

Our institution has permanent access to SNDS data in application of the provisions of articles R. 1461-12 *et seq.* of the French Public Health Code. All analyses were performed by using SAS software, version 9.2 (SAS Institute).

Role of the Funding Source

This research was funded by Caisse Nationale de l'Assurance Maladie (the French national health insurance fund). All of the authors are employees of a public French organization.

RESULTS

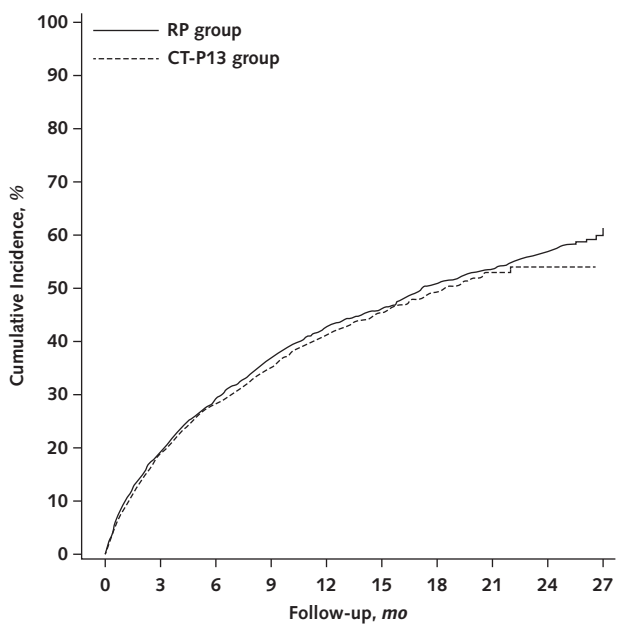
Patient Characteristics

A total of 157 886 individuals with CD were identified in the SNDS: 32.5% based on eligibility for an LTD with a diagnosis of CD, 22.4% based on a CD-related hospitalization, and 45.1% based on both of these criteria. In this population, 6676 patients initiated infliximab therapy between 1 March 2015 and 30 November 2016. Patients were excluded for the following reasons: 393 were younger than 15 years, 18 had no prior utilization of outpatient health care in the 3 years before initiating infliximab therapy, and 1215 had another indication for infliximab (**Figure 1**). Thus, 5050 individuals from 530 hospitals were included in the analysis: 2551 (50.5%) in the RP group and 2499 (49.5%) in the CT-P13 group. The median follow-up was 366 days (IQR, 195 to 605 days) in the RP group and 286 days (IQR, 184 to 432 days) in the CT-P13 group.

Patient characteristics at cohort entry are shown in **Table 1**. The cohort comprised 53.6% women; the median age was 33 years (IQR, 24 to 46 years), median CD duration was 2.3 years (IQR, 0.4 to 7.2 years), 55.4% of patients had at least 1 overnight hospitalization during the previous 12 months, and 40.4% initiated therapy with infliximab in combination with thiopurines. Therapy with RP was more frequently initiated in 2015 (65.3%), and therapy with CT-P13 was more frequently initiated in 2016 (71.7%). The RP was more frequently prescribed in private hospitals than in university hospitals (33.9% vs. 30.9%); CT-P13 was used less frequently in private hospitals than in university hospitals (21.6% vs. 43.6%). Patient characteristics at cohort entry were well balanced but with a trend toward more severe CD in the CT-P13 group; more pelvic or abdominal computed tomography (48.1% vs. 42.5%) or magnetic resonance imaging (50.6% vs. 43.5%), hospitalizations (57.4% vs. 53.4%), and CD-related surgeries (17.7% vs. 14.8%) occurred during the previous 12 months.

During follow-up, 18.6% of patients discontinued infliximab in the RP group and 17.6% of patients dis-

Figure 2. Cumulative incidence plot for event-free survival: primary outcome.



The primary outcome was a composite end point of death, Crohn disease–related surgery, all-cause hospitalization, and reimbursement of another biologic therapy. RP = reference product.

Table 2. Effectiveness

Event	Events/Patients, *n/N*		Incidence Rate per 1000 Person-Years		Multivariable Cox Model	
	RP Group	CT-P13 Group	RP Group	CT-P13 Group	Hazard Ratio (95% CI)	*P* Value
Primary outcome: composite end point*	1147/2551	952/2499	533.9	560.3	0.92 (0.85–0.99)	
All-cause hospitalization†	874/2551	750/2499	392.5	425.4	0.92 (0.83–1.01)	0.088
CD-related hospitalization‡	611/2551	572/2499	253.0	306.7	1.00 (0.90–1.11)	>0.20
CD-related surgery§	284/2551	285/2499	107.6	142.0	1.09 (0.92–1.28)	>0.20
Colon/small-bowel surgery‖	193/2551	190/2499	71.1	92.1	1.10 (0.91–1.34)	>0.20
Dispensing of other biologic therapy¶	406/2551	312/2499	149.7	151.8	0.93 (0.79–1.08)	>0.20

CD = Crohn disease; CT = computed tomography; MRI = magnetic resonance imaging; RP = reference product.
* Multivariable marginal Cox model adjusted for age, CD duration, complementary universal health insurance status, abdominal or pelvic CT, corticosteroids, budesonide, thiopurines, last biologic therapy, all-cause hospitalizations, colon/small bowel surgery and anorectal abscess or fistula surgery.
† Multivariable marginal Cox model adjusted for age, CD site, complementary universal health insurance status, colonoscopy, abdominal or pelvic MRI, abdominal or pelvic CT, corticosteroids, thiopurines, last biologic therapy, all-cause hospitalizations, and colon/small bowel surgery.
‡ Multivariable marginal Cox model adjusted for age, complementary universal health insurance status, colonoscopy, abdominal or pelvic MRI, abdominal or pelvic CT, corticosteroids, thiopurines, last biologic therapy, CD-related hospitalizations, and colon/small bowel surgery.
§ Multivariable marginal Cox model adjusted for sex, CD duration, abdominal or pelvic MRI, abdominal or pelvic CT, last biologic therapy, all-cause hospitalizations, colon/small bowel surgery, and anorectal abscess or fistula surgery.
‖ Multivariable marginal Cox model adjusted for CD duration, CD site, abdominal or pelvic MRI, abdominal or pelvic CT, corticosteroids, budesonide, thiopurines, last biologic therapy, all-cause hospitalizations, and colon/small bowel surgery.
¶ Multivariable marginal Cox model adjusted for sex, CD duration, corticosteroids, thiopurines, last biologic therapy, and all-cause hospitalizations.

continued infliximab in the CT-P13 group, and 6.3% and 8.2% of patients, respectively, switched to the other form of infliximab (**Appendix Table 3**, available at Annals.org).

Effectiveness

The primary outcome did not differ between the RP and CT-P13 groups (log-rank test, $P > 0.20$). The 6-, 12-, and 18-month cumulative incidence rates of the primary outcome were 29.6% (95% CI, 27.8 to 31.4), 43.1% (CI, 41.2 to 45.1), and 51.5% (CI, 49.6 to 53.4), respectively, in the RP group and 28.6% (CI, 26.9 to 30.4), 41.6% (CI, 39.7 to 43.6), and 50.1% (CI, 48.1 to 52.0), respectively, in the CT-P13 group (**Figure 2**). Overall, a composite event was reported in 1147 patients (45.0%), including 838 hospitalizations (32.8%), in the RP group and in 952 patients (38.1%), including 719 hospitalizations (28.8%), in the CT-P13 group (**Appendix Table 3**); 67.6% of hospitalizations were CD-related (**Appendix Table 4**, available at Annals.org).

In multivariable analysis of the primary outcome, CT-P13 was equivalent to RP (HR, 0.92 [CI, 0.85 to 0.99]) (**Table 2** and **Appendix Figure 1**, available at Annals.org). In this multivariable analysis, combination therapy with a thiopurine, with (HR, 0.71 [CI, 0.63 to 0.80]) or without (HR, 0.81 [CI, 0.73 to 0.90]) prior use of thiopurine, and prior colon/small-bowel surgery (HR, 0.68 [CI, 0.56 to 0.83]) were inversely associated with the primary outcome. Prior all-cause hospitalizations (>2 weeks: HR, 2.37 [CI, 2.03 to 2.76]) and prior use of adalimumab (HR, 1.20 [CI, 1.09 to 1.32]), vedolizumab (HR, 1.82 [CI, 1.14 to 2.89]) or ustekinumab (HR, 4.1 [CI, 2.14 to 7.85]) were associated with the primary outcome (**Appendix Table 5**, available at Annals.org).

Because the log-linearity hypothesis was not verified for age, CD duration, nights of CD-related hospitalization (without CD-related surgery) and cumulative corticosteroid dose, these continuous variables were therefore transformed into class variables. There was no evidence against the proportional hazards hypothesis.

Multivariable analysis of secondary outcomes did not reveal any significant differences between CT-P13 and RP in the following events: all-cause hospitalization (HR, 0.92 [CI, 0.83 to 1.01]), CD-related hospitalization (HR, 1.00 [CI, 0.90 to 1.11]), CD-related surgery (HR, 1.09 [CI, 0.92 to 1.28]), CD-related surgery except for anorectal abscess or fistula surgery (HR, 1.10 [CI, 0.91 to 1.34]), and reimbursement of another biologic therapy (HR, 0.93 [CI, 0.79 to 1.08]) (**Table 2** and **Appendix Figures 3** to **10**, available at Annals.org).

No heterogeneity of the primary outcome was observed on an interaction test according to sex ($P > 0.20$), age ($P > 0.20$), CD duration ($P = 0.143$) or type ($P > 0.20$), or exposure to thiopurines ($P > 0.20$) (**Appendix Figure 2**). Sensitivity analyses demonstrated the robustness of the results (**Appendix Tables 6** and **7**, available at Annals.org). The E-value was 1.6 to move the upper bound of the CI for the HR (0.99) of the primary outcome above the predefined upper equivalence limit (1.25), and 1.8 to move the HR estimate to greater than 1.25.

Safety

A total of 198 serious infections were identified, including 47 (24%) skin and subcutaneous tissue infections; 40 (20%) lung infections; and 40 (20%) gastrointestinal infections, including 15 (8%) *Clostridium difficile* infections (**Appendix Table 8**, available at Annals.org). Multivariable analysis did not demonstrate any significant differences between RP and CT-P13 in serious infections (HR, 0.82 [CI, 0.61 to 1.11]) (**Table 3**). Tuberculosis was diagnosed in 6 patients in each group (HR, 1.10 [CI, 0.36 to 3.34]) (**Table 3**). Thirty-eight cases of solid or hematologic cancer were identified: 15 (39%) cases of digestive cancer, including 8 (21%) of colorectal cancer and 4 (11%) of small-bowel cancer, and 4 (11%) cases of hematologic cancer, including 3 (8%) cases of lymphoma (**Appendix Table 9**, available at Annals.org). The median age at cancer diagnosis was 54 years (IQR, 45 to 61 years). Multivariable analysis did

not demonstrate any significant differences between CT-P13 and RP in solid or hematologic cancer (HR, 0.66 [CI, 0.33 to 1.32]) (Table 3).

DISCUSSION

Approval of CT-P13 for CD was based on extrapolation of the results observed in arthritis. Our nationwide observational cohort study of infliximab-naive patients with CD demonstrates equivalent effectiveness of RP and CT-P13. The HR and CI (HR, 0.92 [CI, 0.85-0.99]) were situated within the predefined equivalence margins (0.80 to 1.25), and no significant differences were observed between the 2 groups in serious infections, tuberculosis, and solid or hematologic cancer.

All-cause and CD-related 12-month hospitalization rates were 33.8% and 24.9%, respectively. These rates are similar to those reported after 1 year of follow-up in real-life studies (all-cause, 25% to 34%; CD-related, 19%) (25, 36–38). The CD-related 12-month surgery rate was 11.3%, also similar to previous reports (6% to 12%) (36–38). Combination therapy with a thiopurine, with (HR, 0.71 [CI, 0.63 to 0.80]) or without (HR, 0.81 [CI, 0.73 to 0.90]) prior use of thiopurine, was associated with a lower composite event rate, because combination therapy with a thiopurine has been associated with corticosteroid-free clinical remission in clinical trials (1). The incidence rates of serious infections, tuberculosis, and solid or hematologic cancer (Table 3) corresponded to the expected ranges: 20 to 80 per 1000 person-years (39–43), 0.5 to 15 per 1000 person-years (44–46), and 4 to 8 per 1000 person-years (39, 40, 46), respectively.

Over the past 40 years, new drug approval has been based on randomized, double-blind, controlled trials. However, patients included in these trials are highly selected. One study showed that only 34% of patients with CD seen in clinical practice can be included in trials (47). Studies such as ours assess real-life effectiveness by including all patients receiving treatment with long-term follow-up. Several real-life effectiveness studies in CD have been published (25, 36, 38). One study using data from the OptumLabs Data Warehouse in 3205 anti-TNF–naive patients with CD showed that patients treated with infliximab were less frequently hospitalized, underwent fewer surgeries, and received corticosteroids less often than those treated with adalimumab (25).

Our study has several strengths. First, the SNDS is an almost comprehensive database for drug dispensing, hospitalizations, and surgery in France. Second, this study included an unselected sample of 5050 patients with CD. Third, the equivalence limits were more stringent than those used in randomized controlled trials (10% vs. 15% absolute difference). Fourth, the indication bias was minimal: the 2 groups were well balanced (Table 1), and the choice between CT-P13 or RP was made by the hospital pharmacy, not by the physician. The primary analysis was also performed with the inverse probability of treatment weighting method, which did not modify the results. Fifth, the observed HR of 0.92 could be explained by a confounder associated with both the treatment group and the primary outcome that has a risk ratio of 1.6 or higher. Such a high level of residual confounding is unlikely.

Our study also has limitations. First, the SNDS does not include all relevant clinical data allowing calculation of such indices as the Harvey-Bradshaw Index or Crohn's Disease Activity Index. We therefore used proxies to estimate disease severity. Second, an algorithm was used to identify patients with CD. Other studies have used the same algorithm (19, 22, 48), based on the combination of hospitalization and LTD CD codes. We also used dispensing of infliximab (excluding other indications for anti-TNF therapy). Third, only infliximab-naive patients were included. Another study will need to be conducted to assess the switch from RP to CT-P13 (or vice versa). Fourth, some hospitals only use the biosimilar, whereas others only use the RP. This center effect was taken into account by a marginal model but was probably minor, because sensitivity analysis with a fixed Cox model (without the marginal model) gave very similar results. Fifth, the 95% CI (HR, 0.92 [95% CI, 0.85 to 0.99]) did not contain 1.00, which might suggest the superiority of CT-P13 over RP. However, the CIs for almost all sensitivity analyses included 1.00. Moreover, the equivalence margins were defined in order to be clinically relevant. A minor difference such as that observed in this study is therefore statistically significant (the 95% CI did not contain 1.00) but not clinically relevant (the 95% CI lies within the clinical

Table 3. Safety Analysis

Event	Events/Patients, *n/N*		Incidence Rate per 1000 Person-Years		Cox Model	
	RP Group	CT-P13 Group	RP Group	CT-P13 Group	HR (95% CI)	*P* Value
Serious infection*	115/2551	83/2499	42.3	39.8	0.82 (0.61–1.11)	0.20
Tuberculosis†	6/2551	6/2499	2.1	2.8	1.10 (0.36–3.34)	>0.20
Cancer‡	25/2476	13/2420	6.5	4.9	0.66 (0.33–1.32)	>0.20

CD = Crohn disease; HR = hazard ratio; RP = reference product.
* Multivariable marginal Cox model adjusted for age, CD duration, complementary universal health insurance status, last biologic therapy, and all-cause hospitalizations.
† Marginal Cox model.
‡ Patients with a diagnosis of cancer during the previous 5 y were excluded from the cancer analysis. Patients were censored at study end (30 June 2017), or switch from RP to CT-P13 or from CT-P13 to RP plus 30 d (no censoring after discontinuation of infliximab for the cancer analysis). Multivariable marginal Cox model adjusted for age.

equivalence margins). Finally, because assessment of infliximab dose escalation cannot be reliably assessed with the SNDS (owing to the absence of weight in the database, among other things), dose escalation was not evaluated during follow-up.

In conclusion, our observational study of real-life data suggests that effectiveness of CT-P13 is equivalent to that of RP in infliximab-naive patients. No difference was observed in safety outcomes. The choice between the 2 products can therefore be based on cost only.

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Appendix: Materials and Methods

Data Source

The SNDS contains both the national health insurance information system, the SNIIRAM (Système National d'Information Inter-régimes de l'Assurance Maladie), and the hospital discharge database PMSI (Programme de Médicalisation des Systèmes d'Information). The PMSI database contains all procedures performed during hospital stays, and the principal, related, or associated diagnoses. The principal and related diagnoses correspond to the diseases justifying hospitalization. More specifically, the related diagnosis is used when the patient is hospitalized for administration of a medical treatment, such as infliximab. Diseases are coded according to the ICD-10, and procedures are coded according to the French medical classification for clinical procedures, CCAM (Classification Commune des Actes Médicaux). Patients with LTDs, such as CD, are reimbursed for their health expenditure, and the diagnosis is recorded in the SNDS. Eligibility for LTD is established by a national health insurance expert physician at the request of the patient's general practitioner. The LTDs are recorded with ICD-10 codes and the LTD start date.

Statistical Analysis

In an equivalence study, 2 treatments can be considered to be equivalent when the treatment HR and its CI are situated within the predefined clinical equivalence margins: [Δ − 1/Δ]. The null hypothesis was that the HR and its CI were situated outside the equivalence margins–that is, either lower bound 95% CI(HR) <Δ or upper bound 95% CI(HR) >1/Δ. When the collected data on the HR reject the null hypothesis of nonequivalence, the alternative explanation ($\Delta \leq$ 95%CI(HR) $\leq$1/Δ) that the 2 treatments are equally effective can then be accepted. Equivalence margins in biosimilar arthritis trials were an absolute difference of 15%, and the noninferiority margin in NOR-SWITCH was also 15% (4, 8, 26, 27). Converted into relative margins with an event rate of 55%, these margins correspond to (55 − 15)/55 = 0.727 to 1/0.727 = 1.375, that is [0.727 − 1.375]. We chose an equivalence margin of 10% for an absolute difference because we consider it to be more clinically relevant. Converted into relative margins with an event rate of 40%, equivalence margins of [0.80 − 1.25] were therefore adopted.

Variables entered into the multivariable models were chosen as potential confounding factors and were included as time-independent variables. The marginal Cox model was constructed in several stages. Potential confounding factors were classified into 4 groups according to their order of appearance in the patient's life and clinical care (that is, a chronological and logical order):

1. Constitutional characteristics: sex, age, and CD duration and type.
2. Current social context data: complementary universal health insurance status and deprivation index.
3. Current CD severity (assessed during the 12 months before cohort entry): CD-related imaging, endoscopies, treatments, hospitalizations, and surgeries.
4. Time (semester) of infliximab initiation.

For the first stage, the first group of variables was added to the model, and variables were selected for the next stage only when they were significant at a stringent *P* value of 0.05, in order to avoid spurious results in view of the large sample size. Then, for the second stage, the second group of variables was added to the model together with the variables selected at the first stage. All variables selected at the first stage and variables from the second group when they were significant at a *P* value of 0.05 were included in the third stage, and so on for the subsequent stages. The variables remaining in the last stage were included in the final adjusted model.

There were no missing data for all variables used except for the deprivation index, because it is not calculated for people living outside metropolitan France (overseas department) or for those living in municipalities with fewer than 50 households. Missing data for this categorical variable were considered as a distinct category ("missing"). The log-linearity hypothesis was verified by martingale residuals, and the proportional hazard hypothesis was verified by Schoenfeld residuals.

A sensitivity analysis used the primary outcome analysis with the inverse probability of treatment

weighting (IPTW) method. We created a propensity score defined as the probability of each patient receiving CT-P13 or based on pretreatment variables by logistic regression. We then calculated a stabilized IPTW. For the CT-P13 group, the stabilized IPTW = p/π, and, for the RP group, the stabilized IPTW = $(1 - p)/(1 - \pi)$, where π is the propensity score and p is the probability of treatment without considering covariates (2499/[2499 + 2551]). The level of balance between the CT-P13 and RP groups in the un-weighted sample (original cohort) and in the weighted sample (pseudocohort obtained by inverse probability of treatment weighting) for all factors included in the IPTW analysis was verified by computing the standardized differences. The standardized difference compares the difference in means in units of the pooled SD. A standard difference less than 10% indicates a negligible difference between treatment groups (31–34). A marginal Cox model weighted by the stabilized IPTW was then performed with only 1 explanatory variable: the treatment group.

Appendix Table 1. Disease Identification Algorithms

Disease	ICD-10 Codes	Identification Algorithm
CD	K50	HD (PD/RD, or AD if CD complication in PD/RD) or LTD
CD complications	D500, K56, K60, K61, K624, K625, K630-K632, K650, K922, R104	HD
Ulcerative colitis*	K51	HD or LTD if no newer CD code before infliximab initiation
Rheumatoid arthritis*	M05, M06	HD or LTD
Juvenile rheumatoid arthritis*	M08, M09	HD or LTD
Psoriatic arthritis*	M07	HD or LTD
Ankylosing spondylitis*	M45	HD or LTD
Psoriasis*	L40	HD or LTD
Uveitis, scleritis*	H15, H20, H30, H221, H441	HD or LTD
Sarcoidosis*	D86	HD or LTD
Hidradenitis suppurativa*	L732	HD or LTD
Solid or hematologic cancer	C, D0, D37-D39, D4	2 items among: HD, LTD, radiotherapy or chemotherapy session
Radiation therapy session	Z510	
Chemotherapy session	Z511	
Serious infections (except intestinal or anorectal abscess or fistula)	Reference 20	HD
Tuberculosis	A15-A19, M490, M900, N740, O980	At least 1 dispensing of ≥3 antituberculosis drugs and either another antituberculosis drug dispensing or HD
Childbirth	O80-O84	HD

AD = associated diagnosis; CD = Crohn disease; HD = hospital discharge; ICD-10 = International Classification of Diseases, 10th Revision; PD = principal diagnosis; RD = related diagnosis; LTD = long-term disease.
* Infliximab indication other than CD.

Appendix Table 2. Procedure Identification Algorithms

Procedure	CCAM Codes
Anorectal abscess or fistula surgery*	HJFA013, HJJA001, HJPA001, HJSA001, HKPA001, HKPA002, HKPA004–HKPA008
Colectomy*	HHFA002, HHFA004–HHFA006, HHFA008–HHFA010, HHFA014, HHFA017, HHFA018, HHFA021–HHFA024, HHFA026, HHFA028–HHFA031, HHFC040, HHFC296
Small-bowel resection*	HGFA001, HGFA003–HGFA005, HGFA007, HGFA013, HGFC014, HGFC016, HGFC021
Rectal resection*	HJFA001, HJFA002, HJFA004–HJFA007, HJFA011, HJFA012, HJFA014, HJFA017, HJFA019, HJFC023, HJFC031
Stricturoplasty*	HGAA003, HGAC010
New intestinal stoma*	HGCA001, HGCA005, HGCA008, HGCC003, HGCC015, HGCC026, HHCA002, HHCA003, HHCC007, HHCC011
Colonoscopy	HJQE001–HHQE005, HHAE001, HHFE001, HHFE002, HHFE004, HHFE005, HHFE006
Gastroscopy	HEQE002, HEQE003, HEQE005
Capsule endoscopy	HGQD002
Abdominal or pelvic CT	ZCQH001, ZCQH002, ZCQK004, ZCQK005
Abdominal or pelvic MRI	ZCQJ004, ZCQJ005, ZCQN001, ZCQN002
Anal ultrasonography	HJQJ003

CCAM = Classification Commune des Actes Médicaux [French Common Classification of Procedures]; CT = computed tomography; MRI = magnetic resonance imaging.
* Crohn disease–related surgery.

Appendix Table 3. Follow-up: First Event or First Censoring for Primary Outcome

Variable	All Patients (*n* = 5050)	RP Group (*n* = 2551)	CT-P13 Group (*n* = 2499)
Censoring, *n* (%)			
Total events	2951 (58.4)	1404 (55.0)	1547 (61.9)
Discontinuation of infliximab	914 (18.1)	475 (18.6)	439 (17.6)
Switch of therapy			
Total switches	365 (7.2)	160 (6.3)	205 (8.2)
CT-P13 to Remicade	204 (4.0)	–	204 (8.2)
CT-P13 to SB2	1 (0.0)	–	1 (0.0)
Remicade to CT-P13	160 (3.2)	160 (6.3)	–
Study completion	1672 (33.1)	769 (30.1)	903 (36.1)
Events, *n* (%)			
Total events	2099 (41.6)	1147 (45.0)	952 (38.1)
Hospitalization	1557 (30.8)	838 (32.8)	719 (28.8)
CD-related surgery	162 (3.2)	83 (3.3)	79 (3.2)
Death	5 (0.1)	5 (0.2)	–
Other biologic therapy dispensed	462 (9.1)	267 (10.5)	195 (7.8)
Adalimumab	288 (5.7)	174 (6.8)	114 (4.6)
Vedolizumab	136 (2.7)	75 (2.9)	61 (2.4)
Ustekinumab	38 (0.8)	18 (0.7)	20 (0.8)

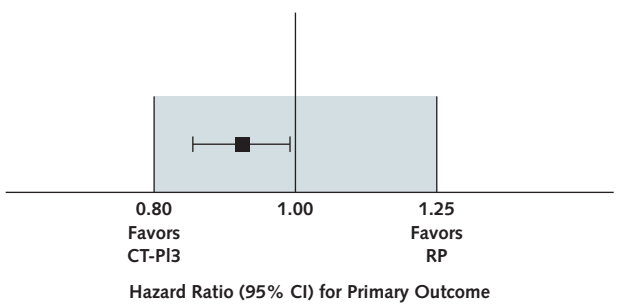
CD = Crohn disease; RP = reference product.

Appendix Table 4. Diagnosis of All-Cause Hospitalizations in the Primary Outcome

Variable	All Patients (*n* = 1557)	RP Group (*n* = 838)	CT-P13 Group (*n* = 719)
CD or CD complications, *n* (%)			
Total events	1053 (67.6)	540 (64.4)	513 (71.3)
CD	592 (38.0)	304 (36.3)	288 (40.1)
Bowel obstruction	123 (7.9)	61 (7.3)	62 (8.6)
Noninfectious gastroenteritis or colitis or digestive symptoms	115 (7.4)	58 (6.9)	57 (7.9)
Anorectal disease	102 (6.6)	49 (5.8)	53 (7.4)
Intestinal abscess, fistula, or perforation	50 (3.2)	26 (3.1)	24 (3.3)
Ulcerative colitis	48 (3.1)	27 (3.2)	21 (2.9)
Infectious gastroenteritis or colitis	23 (1.5)	15 (1.8)	8 (1.1)
Other events, *n* (%)			
Cancer	31 (2.0)	22 (2.6)	9 (1.3)
Urinary tract (infection or stones)	29 (1.9)	16 (1.9)	13 (1.8)
Lung infection	19 (1.2)	10 (1.2)	9 (1.3)
Bile duct disease	18 (1.2)	13 (1.6)	5 (0.7)
Skin infection	18 (1.2)	8 (1.0)	10 (1.4)
Acute pancreatitis	11 (0.7)	4 (0.5)	7 (1.0)
Cardiac arrhythmia	8 (0.5)	6 (0.7)	2 (0.3)
Ankylosing spondylitis	6 (0.4)	4 (0.5)	2 (0.3)
Others (≤5 patients)	364 (23.4)	215 (25.7)	149 (20.7)

CD = Crohn disease; RP = reference product.

Appendix Figure 1. Hazard ratio (95% CI) and equivalence margins for the primary outcome.



The outer lines indicate equivalence margins; the shaded region between a hazard ratio of 0.80 and 1.25 indicates values for which CT-P13 would be considered to be equivalent to the RP. RP = reference product.

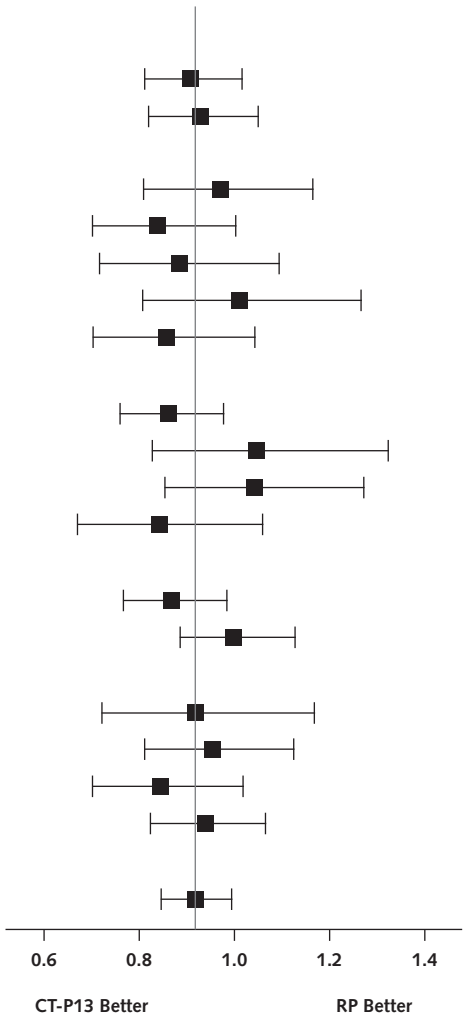
Appendix Table 5. Multivariable Marginal Cox Model for Primary Outcome

Variable	Hazard Ratio (95% CI)	*P* Value
Receipt of CT-P13	0.92 (0.85–0.99)	
Age		<0.001
15–24 y	1.00	
25–34 y	1.03 (0.90–1.17)	
35–44 y	1.06 (0.92–1.21)	
45–54 y	1.19 (1.03–1.38)	
≥55 y	1.39 (1.20–1.60)	
CD duration >3 y*	1.23 (1.13–1.34)	<0.001
Complementary universal health insurance status	1.16 (1.04–1.30)	0.007
Abdominal or pelvic CT†	1.14 (1.03–1.27)	0.013
Drug exposure		
Corticosteroids‡		0.005
0	1.00	
<1 g	0.99 (0.86–1.14)	
1–2 g	1.16 (1.02–1.32)	
2–3 g	1.18 (1.01–1.38)	
>3 g	1.21 (1.07–1.37)	
Budesonide†	1.12 (1.02–1.24)	0.025
Thiopurine		<0.001
None	1	
Prior	0.89 (0.78–1.02)	
Combination therapy	0.81 (0.73–0.90)	
Prior and combination therapy	0.71 (0.63–0.80)	
Last biologic therapy†		<0.001
None	1.00	
Adalimumab	1.20 (1.09–1.32)	
Vedolizumab	1.82 (1.14–2.89)	
Ustekinumab	4.10 (2.14–7.85)	
Duration of all-cause hospitalization†§		<0.001
0 nights	1.00	
<3 nights	1.17 (1.01–1.35)	
3 nights to 1 wk	1.34 (1.15–1.57)	
1–2 wk	1.55 (1.34–1.80)	
>2 wk	2.37 (2.03–2.76)	
Surgery		
Colon/small-bowel surgery†	0.68 (0.56–0.83)	<0.001
Anorectal abscess or fistula surgery†	1.32 (1.12–1.55)	0.001

CD = Crohn disease CT = computed tomography.
* Time since first diagnosis.
† At least once during the 12 mo before cohort entry.
‡ Cumulative prednisone equivalent corticosteroid dose during the 12 mo before cohort entry.
§ Without CD-related surgery.

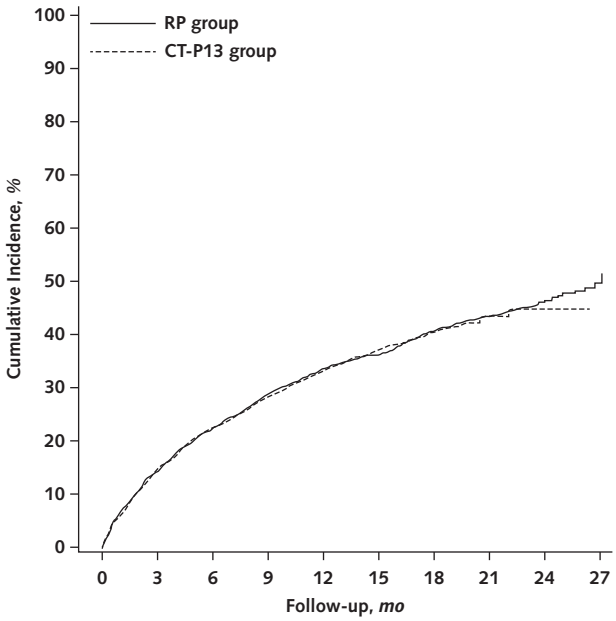
Appendix Figure 2. Forest plot of composite event-free survival.

Subgroup	Patients, *n* (%)	Hazard Ratio (95% CI)	*P* Value*
Sex			>0.20
Women	2706 (53.6)	0.91 (0.81–1.02)	
Men	2344 (46.4)	0.93 (0.82–1.05)	
Age			>0.20
15–24 y	1268 (25.1)	0.97 (0.81–1.16)	
25–34 y	1412 (28.0)	0.84 (0.70–1.00)	
35–44 y	953 (18.9)	0.89 (0.72–1.09)	
45–54 y	685 (13.6)	1.01 (0.81–1.27)	
≥55 y	732 (14.5)	0.86 (0.70–1.04)	
Thiopurine exposure			>0.20
None	2347 (46.5)	0.86 (0.76–0.98)	
Prior	662 (13.1)	1.05 (0.83–1.32)	
Combination therapy	1076 (21.3)	1.04 (0.85–1.27)	
Prior and combination therapy	965 (19.1)	0.84 (0.67–1.06)	
CD duration			0.14
Less than 3 y	2738 (54.2)	0.87 (0.77–0.98)	
More than 3 y	2312 (45.8)	1.00 (0.89–1.13)	
CD site			>0.20
Colon	721 (14.3)	0.92 (0.72–1.17)	
Small bowel	1196 (23.7)	0.96 (0.81–1.12)	
Colon and small bowel	1274 (25.2)	0.85 (0.70–1.02)	
Unspecified	1859 (36.8)	0.94 (0.82–1.07)	
Total	5050 (100)	0.92 (0.85–0.99)	



CD = Crohn disease; RP = reference product.
* Interaction test.

Appendix Figure 3. Cumulative incidence plot for event-free survival: all-cause hospitalization.

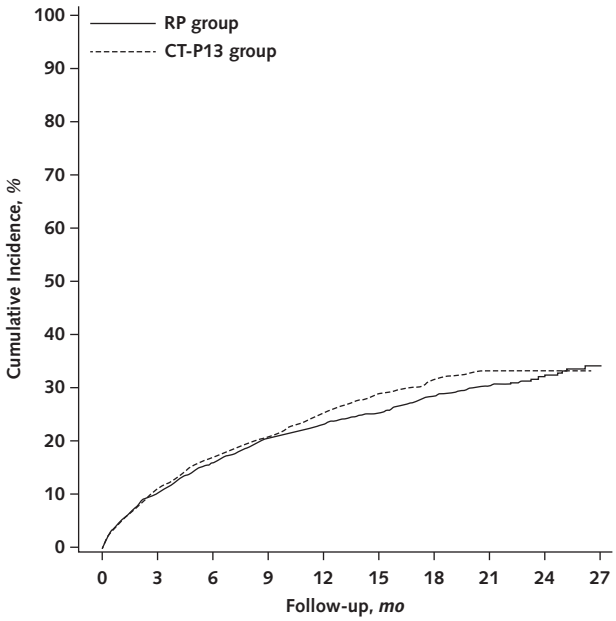


Patients at risk, *n*

RP group	2551	2048	1637	1246	976	769	566	362	196	29
CT-P13 group	2499	1999	1594	1037	674	409	204	70	19	0

RP = reference product.

Appendix Figure 4. Cumulative incidence plot for event-free survival: Crohn disease–related hospitalization.

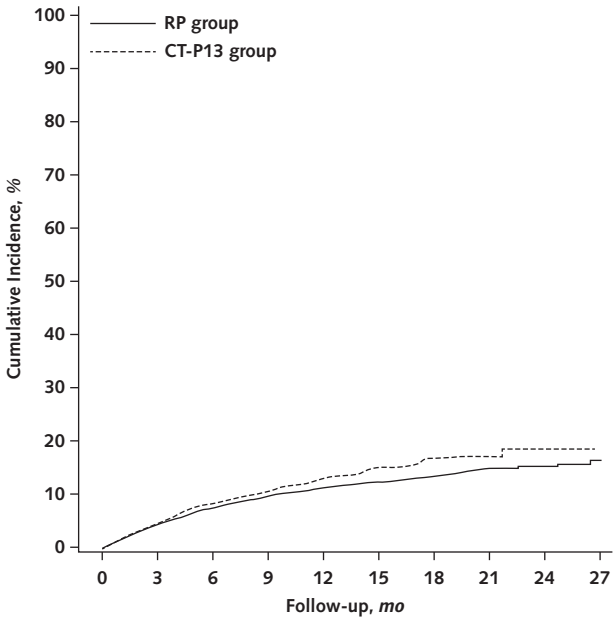


Patients at risk, *n*

RP group	2551	2135	1746	1359	1097	879	660	426	236	33
CT-P13 group	2499	2083	1683	1125	739	454	232	82	20	0

RP = reference product.

Appendix Figure 5. Cumulative incidence plot for event-free survival: Crohn disease–related surgery.

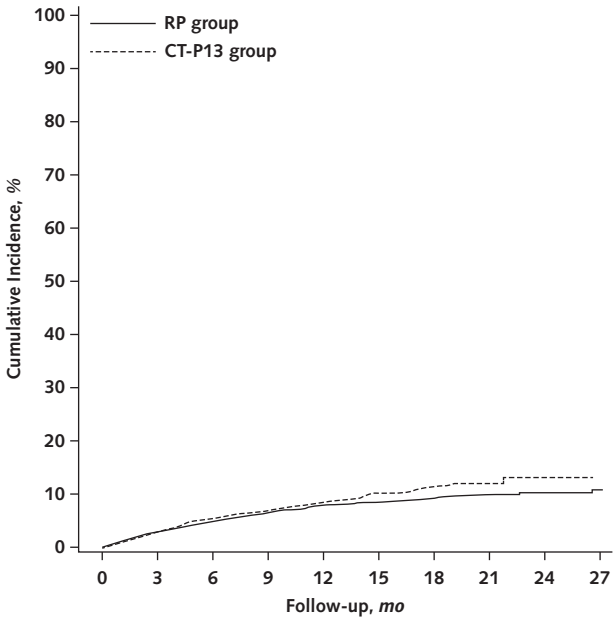


Patients at risk, *n*

RP group	2551	2284	1908	1502	1216	988	758	490	271	40
CT-P13 group	2499	2221	1830	1229	821	505	252	84	20	0

RP = reference product.

Appendix Figure 6. Cumulative incidence plot for event-free survival: colon/small-bowel surgery.

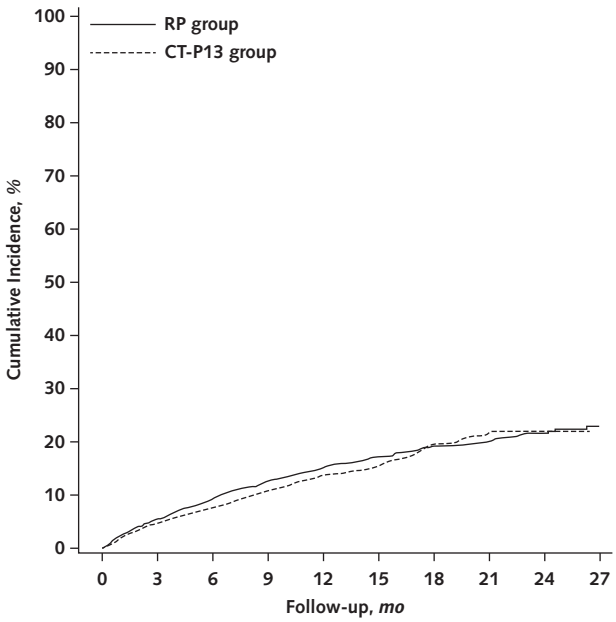


Patients at risk, *n*

RP group	2551	2314	1958	1553	1258	1026	793	522	286	43
CT-P13 group	2499	2261	1886	1279	864	531	265	87	20	0

RP = reference product.

Appendix Figure 7. Cumulative incidence plot for event-free survival: dispensing of another biologic therapy.

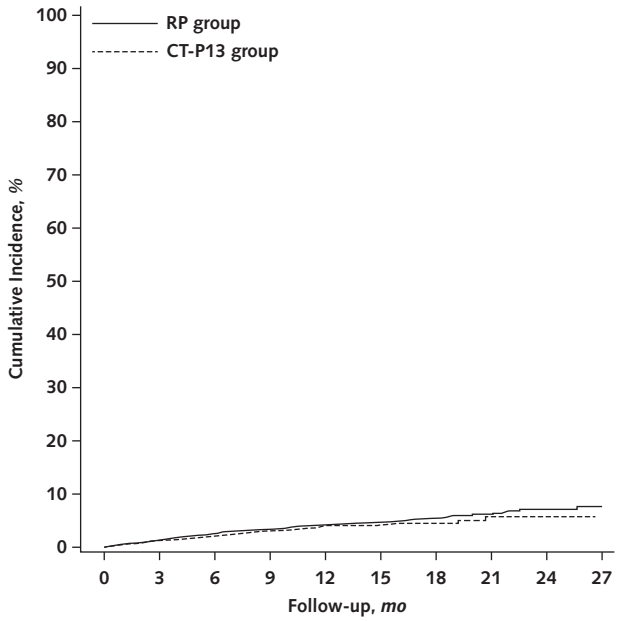


Patients at risk, *n*

RP group	2551	2271	1940	1561	1267	1029	807	540	295	47
CT-P13 group	2499	2221	1880	1284	867	540	264	90	20	0

RP = reference product.

Appendix Figure 8. Cumulative incidence plot for event-free survival: serious infection.

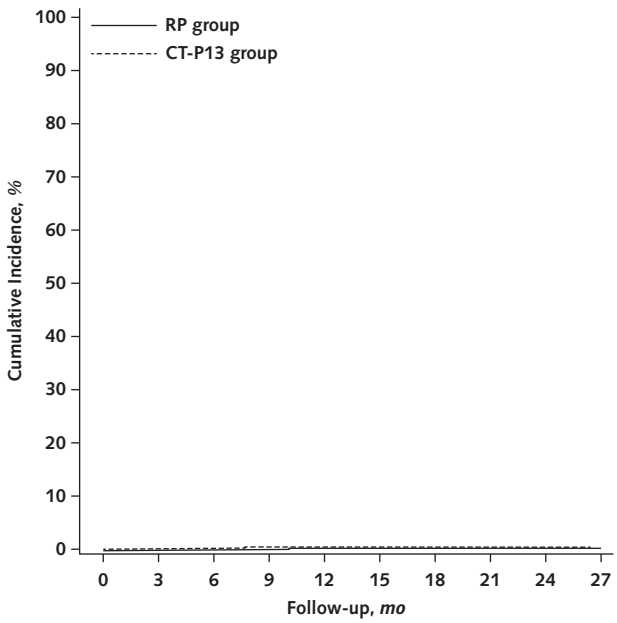


Patients at risk, *n*

RP group	2551	2344	1971	1565	1257	1019	787	523	282	44
CT-P13 group	2499	2292	1911	1286	870	542	271	88	20	0

RP = reference product.

Appendix Figure 9. Cumulative incidence plot for event-free survival: tuberculosis.

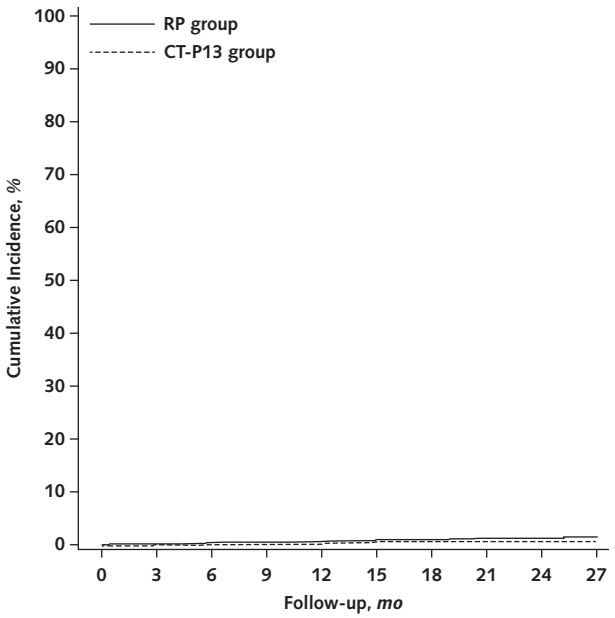


Patients at risk, *n*

RP group	2551	2376	2016	1610	1300	1056	824	547	298	47
CT-P13 group	2499	2322	1943	1320	896	557	279	91	20	0

RP = reference product.

Appendix Figure 10. Cumulative incidence plot for event-free survival: cancer.



Patients at risk, *n*

RP group	2476	2409	2370	2168	1965	1738	1496	1138	718	167
CT-P13 group	2420	2321	2251	1775	1327	903	532	220	85	57

RP = reference product.

Appendix Table 6. Sensitivity Analysis

Variable	Events/Patient, *n/n*		Incidence Rate per 1000 Person-Years		Cox Model	
	RP Group	CT-P13 Group	RP Group	CT-P13 Group	Hazard Ratio (95% CI)	*P* Value
Start of follow-up: first infliximab*	1207/2551	1026/2499	533.4	565.4	0.93 (0.86–1.01)	0.075
End of follow-up: 56 + 30 d*	1060/2551	897/2499	528.8	558.9	0.92 (0.85–1.01)	0.069
End of follow-up: 56 + 90 d*	1179/2551	993/2499	531.2	568.9	0.94 (0.86–1.02)	0.122
No marginal model*	1147/2551	952/2499	533.9	560.3	0.92 (0.84–1.00)	0.054
No infliximab since 2009*†	1100/2439	945/2477	530.0	560.2	0.92 (0.85–1.00)	0.052
IPTW‡	1147/2551	952/2499	533.9	560.3	0.92 (0.84–0.99)	0.035

CD = Crohn disease; IPTW = inverse probability of treatment weighting; RP = reference product.
* Multivariable marginal Cox model adjusted for age, CD duration, complementary universal health insurance status, abdominal or pelvic computed tomography, corticosteroids, budesonide, thiopurines, last biologic therapy, all-cause hospitalizations, colon/small-bowel surgery and anorectal abscess or fistula surgery.
† Excluding patients who received infliximab between 1 January 2009 and 12 mo before initiation of infliximab.
‡ Marginal Cox model weighted by the stabilized IPTW. Results of the IPTW analysis were identical with weights or stabilized weights and with or without truncated weights (weights that exceed the 1st and 99th percentiles of the weights are each set to that percentile value).

Appendix Table 7. Demographic and Baseline Patient Characteristics in the Original Study Cohort and in the Pseudocohort Obtained by Inverse Probability of Treatment Weighting

Variable	Original Cohort			Pseudocohort		
	RP Group (n = 2551), n (%)	CT-P13 Group (n = 2499), n (%)	Standardized Difference, %¶	RP Group (n = 2551), n (%)	CT-P13 Group (n = 2499), n (%)	Standardized Difference, %¶
Age						
15–24 y	683 (26.8)	585 (23.4)	–7.76	641 (25.1)	626 (25.1)	–0.12
25–34 y	717 (28.1)	695 (27.8)	–0.67	711 (27.9)	698 (27.9)	0.09
35–44 y	486 (19.1)	467 (18.7)	–0.92	479 (18.8)	469 (18.8)	0.00
45–54 y	315 (12.4)	370 (14.8)	7.19	346 (13.6)	340 (13.6)	0.15
≥55 y	350 (13.7)	382 (15.3)	4.46	374 (14.7)	366 (14.7)	–0.06
CD duration >3 y*	1213 (47.6)	1099 (44.0)	–7.17	1171 (45.9)	1145 (45.8)	–0.20
Complementary universal health insurance status	365 (14.3)	370 (14.8)	1.42	374 (14.7)	365 (14.6)	-0.14
Abdominal or pelvic CT†	1085 (42.5)	1201 (48.1)	11.13	1157 (45.4)	1135 (45.4)	0.10
Drug exposure						
Budesonide†	571 (22.4)	593 (23.7)	3.21	587 (23.0)	576 (23.0)	0.05
Corticosteroids‡						
0	1031 (40.4)	1019 (40.8)	0.73	1028 (40.3)	1007 (40.3)	–0.02
<1 g	407 (16.0)	352 (14.1)	–5.21	384 (15.0)	376 (15.0)	0.00
1 to 2 g	351 (13.8)	411 (16.5)	7.52	387 (15.2)	379 (15.2)	–0.08
2 to 3 g	243 (9.5)	251 (10.0)	1.72	251 (9.8)	245 (9.8)	–0.07
>3 g	519 (20.3)	466 (18.7)	–4.27	501 (19.7)	492 (19.7)	0.13
Thiopurine						
None	1230 (48.2)	1117 (44.7)	–7.06	1184 (46.4)	1161 (46.5)	0.04
Prior	352 (13.8)	310 (12.4)	–4.15	336 (13.2)	328 (13.1)	–0.09
Combination therapy	456 (17.9)	620 (24.8)	16.97	540 (21.2)	530 (21.2)	0.12
Prior and combination therapy	513 (20.1)	452 (18.1)	–5.14	490 (19.2)	480 (19.2)	–0.05
Last biologic therapy†						
None	1827 (71.6)	1777 (71.1)	–1.13	1815 (71.2)	1779 (71.2)	0.07
Adalimumab	678 (26.6)	696 (27.9)	2.85	699 (27.4)	684 (27.4)	–0.09
Vedolizumab	36 (1.4)	23 (0.9)	–4.57	30 (1.2)	30 (1.2)	0.19
Ustekinumab	10 (0.4)	3 (0.1)	–5.36	7 (0.3)	6 (0.3)	–0.20
Duration of all-cause hospitalization†§						
0 nights	1189 (46.6)	1065 (42.6)	–8.03	1137 (44.6)	1113 (44.6)	–0.04
<3 nights	367 (14.4)	335 (13.4)	–2.83	355 (13.9)	349 (14.0)	0.12
3 nights to 1 wk	358 (14.0)	341 (13.7)	–1.10	354 (13.9)	346 (13.9)	–0.03
1 to 2 wk	314 (12.3)	356 (14.3)	5.72	340 (13.4)	333 (13.3)	–0.26
>2 wk	323 (12.7)	402 (16.1)	9.79	365 (14.3)	358 (14.3)	0.06
Surgery						
Colon/small-bowel surgery†	137 (5.4)	159 (6.4)	4.21	148 (5.8)	146 (5.8)	0.04
Anorectal abscess or fistula surgery†	239 (9.4)	282 (11.3)	6.28	259 (10.2)	255 (10.2)	0.13

CD = Crohn disease; CT = computed tomography; RP = reference product.
* Time from first diagnosis.
† At least once during the 12 mo before cohort entry.
‡ Cumulative prednisone equivalent corticosteroid dose during the 12 mo before cohort entry.
§ Without CD-related surgery.
¶ The standardized difference compares the difference in means in units of the pooled standard deviation. A standard difference less than 10% indicates a negligible difference between treatment groups.

Appendix Table 8. Serious Infectious Events

Site of Infection	All Patients (*n* = 198), *n* (%)	RP Group (*n* = 115), *n* (%)	CT-P13 Group (*n* = 83), *n* (%)
Skin and subcutaneous tissue	47 (24)	26 (23)	21 (25)
Lung	40 (20)	22 (19)	18 (22)
Gastrointestinal tract	40 (20)	23 (20)	17 (20)
Clostridium difficile	15 (8)	9 (8)	6 (7)
Urinary tract	26 (13)	15 (13)	11 (13)
Ear, nose, throat	6 (3)	5 (4)	1 (1)
Musculoskeletal	2 (1)	1 (1)	1 (1)
Other	37 (19)	23 (20)	14 (17)

RP = reference product.

Appendix Table 9. Solid or Hematologic Cancer

Site of Cancer	All Patients (*n* = 38), *n* (%)	RP Group (*n* = 25), *n* (%)	CT-P13 Group (*n* = 13), *n* (%)
Gastrointestinal tract	15 (39)	10 (40)	5 (38)
Colorectal	8 (21)	6 (24)	2 (15)
Small bowel	4 (11)	2 (8)	2 (15)
Urinary tract	5 (13)	2 (8)	3 (23)
Hematologic cancer	4 (11)	2 (8)	2 (15)
Lymphoma	3 (8)	1 (4)	2 (15)
Breast	3 (8)	2 (8)	1 (8)
Lung	3 (8)	2 (8)	1 (8)
Uterus	3 (8)	3 (12)	–
Skin	2 (5)	1 (4)	1 (8)
Cervix	2 (5)	2 (8)	–
Thyroid	1 (3)	1 (4)	–

RP = reference product.