

**Sponsor**

Novartis

**Generic Drug Name**

Adalimumab and infliximab biosimilars

**Trial Indication(s)**

Crohn's disease

**Protocol Number**

CGPN017A2001

**Protocol Title**

GIANT – A multicenter, prospective, observational study of real-world anti-TNF $\alpha$  treatment regimens of Hyrimoz<sup>TM</sup> (adalimumab biosimilar) or Zessly<sup>TM</sup> (infliximab biosimilar) in patients with Crohn's Disease

**Clinical Trial Phase**

NA

**Phase of Drug Development**

Phase IV

**Study Start/End Dates**

24 Jun 2019 to 08 May 2020

**Reason for Termination**

This observational study was prematurely terminated at the end of April 2020. The main factors leading to the study termination comprised recent changes in the therapeutic and biosimilar landscape, and the temporary stop in patient recruitment due to the COVID-19 pandemic.

**Study Design/Methodology**

This study was a prospective, multicenter, open-label, observational, non-interventional, patient cohort study with a parallel group design. 1,600 planned adult biologic-naïve patients commencing and routinely receiving either Hyrimoz or Zessly were to be enrolled and treated under real-world conditions.

**Centers**

18 centers in 5 countries: Austria (3), Germany (10), Spain (2), Poland (2), Sweden (1).

**Objectives:**

The early termination of the study led to the recruitment of a limited number of patients and to the collection of a restricted amount of data. The primary and secondary objectives contain only the results of those analyses rendered suitable by the reduced size of the data.

**Primary objective(s)**

To evaluate the effectiveness of Hyrimoz or Zessly in patients with moderate-to-severe Crohn's Disease (CD) in a real-world-setting.

**Secondary objective(s)**

- To assess the validity of the inflammatory bowel disease (IBD) index over an observation period of up to 4 years
- To assess the safety profiles (including adverse events of special interest) of Hyrimoz or Zessly
- To assess the diagnostic and treatment-monitoring value of imaging and disease-related laboratory parameters in patients receiving Hyrimoz or Zessly over an observation period of up to 4 years
- To assess quality of life (QoL) of patients receiving Hyrimoz or Zessly over an observation period of up to 4 years

- To assess pharmaco-economics for Hyrimoz or Zessly collating QoL data and work productivity data based on quality-adjusted life year (QALY) over an observation period of up to 4 years

### **Test Product (s), Dose(s), and Mode(s) of Administration**

Hyrimoz or Zessly were administered according to the label and local guidelines and at the discretion of the investigator.

### **Statistical Methods**

The statistical methods applied to the data collected until premature termination of the study were as follows:

Quantitative data (e.g., age, body weight, etc.) were summarized by appropriate descriptive statistics (i.e. mean, median, standard deviation (SD), minimum, maximum, and 1st and 3rd quartile). All demographic and baseline disease characteristics data (age, gender, predominant race, ethnicity, height, weight, body mass index (BMI), and CD history) were summarized by study treatment.

The summary of duration of exposure to study treatment includes categorical summaries and continuous summaries (i.e. mean, standard deviation etc.) using appropriate units of time. The full analysis set (FAS) was used for all baseline and demographic summaries, as well as for listings. All study treatments, concomitant medications and all safety analyses were summarized by all patients and by study treatment using the safety analysis set (SAF). Adverse events (AEs) summaries included all AEs occurring during the treatment period. The overall AE summaries on or after the first date of administration of investigational drug were produced by study treatment and total patients. For IBD index and Harvey-Bradshaw index (HBI), categorical summaries by visit and treatment group were provided for each descriptor of HBI and for each attribute IBD index. Categorical summaries by visit and treatment group were provided for each question of sIBDQ. WPAI scores for each question were summarized by visit and treatment group. Summary statistics for EQ-5D-5L and SF-MPQ are displayed by visit and treatment group in a table.

### **Study Population: Key Inclusion/Exclusion Criteria**

Inclusion criteria

1. Confirmed diagnosis of CD
2. Treatment failure upon steroids/topical budesonide with or without immunosuppressants
3.  $HBI \geq 5$

4. Males and females as defined as adults ( $\geq 18$  years of age) at enrollment
5. Biologic-naïve status (with the exception of patients receiving Hyrimoz or Zessly for up to 3 months prior to enrollment according to the label and at the discretion of the investigator)
6. Provision of signed informed consent form (consenting)

Exclusion criteria

1. CD in clinical remission ( $\text{HBI} < 5$ )
2. Hemoglobin  $< 8.5$  g/dL
3. Imminent risk of scheduled intestinal surgery (stenosis, strictures, internal fistula)
4. Any contraindications to Hyrimoz or Zessly according to the prescribing recommendations in each country
5. Participation in an interventional clinical trial for immune-mediated inflammatory diseases (IMIDs) or having received any investigational agent or procedure within 30 days prior to enrollment (consenting)

**Participant Flow Table**

| <b>Disposition and reason for discontinuation</b> | <b>Hyrimoz<br/>n (%)</b> | <b>Zessly<br/>n (%)</b> | <b>Total<br/>n (%)</b> |
|---|--------------------------|-------------------------|------------------------|
| Screened set                                      |                          |                         | 63                     |
| Enrolled analysis set                             |                          |                         | 60                     |
| Full analysis set                                 | 47 (100)                 | 13 (100)                | 60 (100)               |
| EM1 analysis set                                  | 38 (80.9)                | 12 (92.3)               | 50 (83.3)              |
| EM2 analysis set                                  | 16 (34.0)                | 7 (53.8)                | 23 (38.3)              |
| Safety analysis set                               | 47 (100)                 | 13 (100)                | 60 (100)               |
| The first 2-years treatment period                |                          |                         |                        |
| Completed 2-years treatment                       | 0                        | 0                       | 0                      |
| Discontinued within 2-years treatment             | 47 (100)                 | 13 (100)                | 60 (100)               |
| Reason for discontinuation                        |                          |                         |                        |
| Physician decision                                | 1 (2.1)                  | 1 (7.7)                 | 2 (3.3)                |
| Subject decision                                  | 2 (4.3)                  | 0                       | 2 (3.3)                |
| Study terminated by sponsor                       | 44 (93.6)                | 12 (92.3)               | 56 (93.3)              |

EM1 = QoL

EM2 = Imaging

Percentages of EM1 and EM2 analysis set are based on FAS.

Percentages of completed 2-years treatment and discontinued within 2-years treatment are based on full analysis set.

## Baseline Characteristics

### Patient demographics (Full analysis set)

| Characteristic         | Hyrimoz<br>N=47 | Zessly<br>N=13 | Total<br>N=60 |
|------------------------|-----------------|----------------|---------------|
| Age (years)            |                 |                |               |
| n                      | 47              | 13             | 60            |
| Mean                   | 39.6            | 35.6           | 38.7          |
| SD                     | 14.19           | 10.97          | 13.57         |
| Median                 | 36.0            | 32.0           | 36.0          |
| Sex -n (%)             |                 |                |               |
| Male                   | 21 (44.7)       | 6 (46.2)       | 27 (45.0)     |
| Female                 | 26 (55.3)       | 7 (53.8)       | 33 (55.0)     |
| Ethnicity -n (%)       |                 |                |               |
| Hispanic or Latino     | 1 (2.1)         | 0              | 1 (1.7)       |
| Not Hispanic or Latino | 45 (95.7)       | 13 (100)       | 58 (96.7)     |
| Unknown                | 1 (2.1)         | 0              | 1 (1.7)       |

## Primary Outcome Result(s)

The early termination of the study led to the recruitment of a limited number of patients and to the collection of a restricted amount of data. The following sections contain only the results of those analyses rendered suitable by the reduced size of the data.

### Summary of Harvey-Bradshaw index (HBI) by visit (Full analysis set)

| Visit      | Descriptor                      | Description               | Hyrimoz<br>N=47 | Zessly<br>N=13 | Total<br>N=60 |
|------------|---------------------------------|---------------------------|-----------------|----------------|---------------|
| Enrollment | General well-being -n (%)       | Very well (+0)            | 0               | 0              | 0             |
|            |                                 | Slightly below par (+1)   | 11 (23.4)       | 3 (23.1)       | 14 (23.3)     |
|            |                                 | Poor (+2)                 | 7 (14.9)        | 4 (30.8)       | 11 (18.3)     |
|            |                                 | Very poor (+3)            | 4 (8.5)         | 3 (23.1)       | 7 (11.7)      |
|            |                                 | Terrible (+4)             | 1 (2.1)         | 1 (7.7)        | 2 (3.3)       |
|            | Abnormal pain -n (%)            | None (+0)                 | 1 (2.1)         | 1 (7.7)        | 2 (3.3)       |
|            |                                 | Mild (+1)                 | 5 (10.6)        | 2 (15.4)       | 7 (11.7)      |
|            |                                 | Moderate (+2)             | 17 (36.2)       | 6 (46.2)       | 23 (38.3)     |
|            |                                 | Severe (+3)               | 0               | 2 (15.4)       | 2 (3.3)       |
|            | Number of liquid stools per day | n                         | 23              | 11             | 34            |
|            |                                 | Mean                      | 5.2             | 5.5            | 5.3           |
|            |                                 | SD                        | 3.23            | 4.41           | 3.59          |
|            | Abdominal mass -n (%)           | None (+0)                 | 17 (36.2)       | 3 (23.1)       | 20 (33.3)     |
|            |                                 | Dubious (+1)              | 4 (8.5)         | 5 (38.5)       | 9 (15.0)      |
|            |                                 | Definite (+2)             | 2 (4.3)         | 3 (23.1)       | 5 (8.3)       |
|            |                                 | Definite and tender (+3)  | 0               | 0              | 0             |
|            | Complications -n (%)            | Athralgia (+1)            | 8 (17.0)        | 2 (15.4)       | 10 (16.7)     |
|            |                                 | Uveitis (+1)              | 1 (2.1)         | 0              | 1 (1.7)       |
|            |                                 | Erythema nodosum (+1)     | 0               | 1 (7.7)        | 1 (1.7)       |
|            |                                 | Aphthous ulcer (+1)       | 1 (2.1)         | 0              | 1 (1.7)       |
|            |                                 | Pyoderma gangrenosum (+1) | 0               | 0              | 0             |

| Visit  | Descriptor                      | Description               | Hyrimoz<br>N=47 | Zessly<br>N=13 | Total<br>N=60 |
|--------|---------------------------------|---------------------------|-----------------|----------------|---------------|
| Week 8 | General well-being -n (%)       | Anal fissure (+1)         | 1 (2.1)         | 2 (15.4)       | 3 (5.0)       |
|        |                                 | New fistula (+1)          | 1 (2.1)         | 2 (15.4)       | 3 (5.0)       |
|        |                                 | Abscess (+1)              | 1 (2.1)         | 1 (7.7)        | 2 (3.3)       |
|        |                                 | Very well (+0)            | 8 (17.0)        |                | 8 (13.3)      |
|        |                                 | Slightly below par (+1)   | 5 (10.6)        |                | 5 (8.3)       |
|        |                                 | Poor (+2)                 | 3 (6.4)         |                | 3 (5.0)       |
|        |                                 | Very poor (+3)            | 0               |                | 0             |
|        |                                 | Terrible (+4)             | 0               |                | 0             |
|        | Abnormal pain -n (%)            | None (+0)                 | 10 (21.3)       |                | 10 (16.7)     |
|        |                                 | Mild (+1)                 | 3 (6.4)         |                | 3 (5.0)       |
|        |                                 | Moderate (+2)             | 3 (6.4)         |                | 3 (5.0)       |
|        |                                 | Severe (+3)               | 0               |                | 0             |
|        | Number of liquid stools per day | n                         | 16              |                | 16            |
|        |                                 | Mean                      | 1.9             |                | 1.9           |
|        |                                 | SD                        | 2.45            |                | 2.45          |
|        | Abdominal mass -n (%)           | None (+0)                 | 14 (29.8)       |                | 14 (23.3)     |
|        |                                 | Dubious (+1)              | 2 (4.3)         |                | 2 (3.3)       |
|        |                                 | Definite (+2)             | 0               |                | 0             |
|        |                                 | Definite and tender (+3)  | 0               |                | 0             |
|        | Complications -n (%)            | Athralgia (+1)            | 4 (8.5)         |                | 4 (6.7)       |
|        |                                 | Uveitis (+1)              | 0               |                | 0             |
|        |                                 | Erythema nodosum (+1)     | 0               |                | 0             |
|        |                                 | Aphthous ulcer (+1)       | 0               |                | 0             |
|        |                                 | Pyoderma gangrenosum (+1) | 0               |                | 0             |
|        |                                 | Anal fissure (+1)         | 1 (2.1)         |                | 1 (1.7)       |
|        |                                 | New fistula (+1)          | 0               |                | 0             |



| Visit       | Descriptor                      | Description               | Hyrimoz<br>N=47 | Zessly<br>N=13 | Total<br>N=60 |
|-------------|---------------------------------|---------------------------|-----------------|----------------|---------------|
| Week 14     | General well-being -n (%)       | Abscess (+1)              | 0               |                | 0             |
|             |                                 | Very well (+0)            |                 | 3 (23.1)       | 3 (5.0)       |
|             |                                 | Slightly below par (+1)   |                 | 2 (15.4)       | 2 (3.3)       |
|             |                                 | Poor (+2)                 |                 | 0              | 0             |
|             |                                 | Very poor (+3)            |                 | 0              | 0             |
|             |                                 | Terrible (+4)             |                 | 0              | 0             |
|             | Abnormal pain -n (%)            | None (+0)                 |                 | 4 (30.8)       | 4 (6.7)       |
|             |                                 | Mild (+1)                 |                 | 1 (7.7)        | 1 (1.7)       |
|             |                                 | Moderate (+2)             |                 | 0              | 0             |
|             |                                 | Severe (+3)               |                 | 0              | 0             |
|             | Number of liquid stools per day | n                         |                 | 5              | 5             |
|             |                                 | Mean                      |                 | 1.6            | 1.6           |
|             |                                 | SD                        |                 | 2.07           | 2.07          |
|             | Abdominal mass -n (%)           | None (+0)                 |                 | 5 (38.5)       | 5 (8.3)       |
|             |                                 | Dubious (+1)              |                 | 0              | 0             |
|             |                                 | Definite (+2)             |                 | 0              | 0             |
|             |                                 | Definite and tender (+3)  |                 | 0              | 0             |
|             | Complications -n (%)            | Athralgia (+1)            |                 | 0              | 0             |
|             |                                 | Uveitis (+1)              |                 | 0              | 0             |
|             |                                 | Erythema nodosum (+1)     |                 | 0              | 0             |
|             |                                 | Aphthous ulcer (+1)       |                 | 0              | 0             |
|             |                                 | Pyoderma gangrenosum (+1) |                 | 0              | 0             |
|             |                                 | Anal fissure (+1)         |                 | 1 (7.7)        | 1 (1.7)       |
|             |                                 | New fistula (+1)          |                 | 1 (7.7)        | 1 (1.7)       |
|             |                                 | Abscess (+1)              |                 | 0              | 0             |
|             |                                 | Very well (+0)            |                 | 0              | 0             |
| Disposition | General well-being -n (%)       |                           |                 |                |               |

| Visit | Descriptor                      | Description               | Hyrimoz<br>N=47 | Zessly<br>N=13 | Total<br>N=60 |
|-------|---------------------------------|---------------------------|-----------------|----------------|---------------|
|       |                                 | Slightly below par (+1)   | 1 (2.1)         | 0              | 1 (1.7)       |
|       |                                 | Poor (+2)                 | 0               | 0              | 0             |
|       |                                 | Very poor (+3)            | 0               | 0              | 0             |
|       |                                 | Terrible (+4)             | 0               | 0              | 0             |
|       | Abnormal pain -n (%)            | None (+0)                 | 0               | 0              | 0             |
|       |                                 | Mild (+1)                 | 0               | 0              | 0             |
|       |                                 | Moderate (+2)             | 1 (2.1)         | 0              | 1 (1.7)       |
|       |                                 | Severe (+3)               | 0               | 0              | 0             |
|       | Number of liquid stools per day | n                         | 1               |                | 1             |
|       |                                 | Mean                      | 4.0             |                | 4.0           |
|       |                                 | SD                        |                 |                |               |
|       | Abdominal mass -n (%)           | None (+0)                 | 1 (2.1)         | 0              | 1 (1.7)       |
|       |                                 | Dubious (+1)              | 0               | 0              | 0             |
|       |                                 | Definite (+2)             | 0               | 0              | 0             |
|       |                                 | Definite and tender (+3)  | 0               | 0              | 0             |
|       | Complications -n (%)            | Athralgia (+1)            | 0               | 0              | 0             |
|       |                                 | Uveitis (+1)              | 0               | 0              | 0             |
|       |                                 | Erythema nodosum (+1)     | 0               | 0              | 0             |
|       |                                 | Aphthous ulcer (+1)       | 0               | 0              | 0             |
|       |                                 | Pyoderma gangrenosum (+1) | 0               | 0              | 0             |
|       |                                 | Anal fissure (+1)         | 0               | 0              | 0             |
|       |                                 | New fistula (+1)          | 0               | 0              | 0             |
|       |                                 | Abscess (+1)              | 0               | 0              | 0             |

Percentages are based on total number per visit per treatment group in full analysis set.

## Secondary Outcome Result(s)

The early termination of the study led to the recruitment of a limited number of patients and to the collection of a restricted amount of data. The following sections contain only the results of those analyses rendered suitable by the reduced size of the data.

### Summary of inflammatory bowel disease (IBD) index by visit (Full analysis set)

| Visit      | Attribute              | Level                     | Hyrmoz<br>N=47<br>n (%) | Zessly<br>N=13<br>n (%) | Total<br>N=60<br>n (%) |
|------------|------------------------|---------------------------|-------------------------|-------------------------|------------------------|
| Enrollment | Mucosal Lesions        | No (+0)                   | 5 (10.6)                | 0                       | 5 (8.3)                |
|            |                        | Small (+6)                | 0                       | 0                       | 0                      |
|            |                        | Large or deep (+16)       | 0                       | 1 (7.7)                 | 1 (1.7)                |
|            | Fistula                | No (+0)                   | 4 (8.5)                 | 1 (7.7)                 | 5 (8.3)                |
|            |                        | Yes (+11)                 | 1 (2.1)                 | 0                       | 1 (1.7)                |
|            | Perianal abscess       | No (+0)                   | 5 (10.6)                | 1 (7.7)                 | 6 (10.0)               |
|            |                        | Yes (+10)                 | 0                       | 0                       | 0                      |
|            | Intestinal resections  | No (+0)                   | 5 (10.6)                | 0                       | 5 (8.3)                |
|            |                        | <40 cm (+2)               | 0                       | 1 (7.7)                 | 1 (1.7)                |
|            |                        | >=40 cm (+7)              | 0                       | 0                       | 0                      |
|            | Stoma                  | No (+0)                   | 5 (10.6)                | 1 (7.7)                 | 6 (10.0)               |
|            |                        | Yes (+11)                 | 0                       | 0                       | 0                      |
|            | Disease extent         | Limited disease (+0)      | 5 (10.6)                | 1 (7.7)                 | 6 (10.0)               |
|            |                        | Extensive disease (+6)    | 0                       | 0                       | 0                      |
|            | Frequency loose stools | <10 per week (+0)         | 5 (10.6)                | 1 (7.7)                 | 6 (10.0)               |
|            |                        | At least 10 per week (+6) | 0                       | 0                       | 0                      |
|            | Stricture              | No (+0)                   | 5 (10.6)                | 0                       | 5 (8.3)                |
|            |                        | Yes (+5)                  | 0                       | 1 (7.7)                 | 1 (1.7)                |
|            | CRP level              | 1-3 mg/L (+0)             | 4 (8.5)                 | 0                       | 4 (6.7)                |
|            |                        | 3-5 mg/L (+2)             | 0                       | 0                       | 0                      |

| Visit  | Attribute             | Level                     | Hyrimoz<br>N=47<br>n (%) | Zessly<br>N=13<br>n (%) | Total<br>N=60<br>n (%) |
|--------|-----------------------|---------------------------|--------------------------|-------------------------|------------------------|
| Week 8 | Biologics use         | above 5 mg/L (+5)         | 1 (2.1)                  | 1 (7.7)                 | 2 (3.3)                |
|        |                       | No (+0)                   | 5 (10.6)                 | 1 (7.7)                 | 6 (10.0)               |
|        |                       | Yes and improved (+2)     | 0                        | 0                       | 0                      |
|        |                       | Yes but not improved (+5) | 0                        | 0                       | 0                      |
|        | Daily activity impact | No (+0)                   | 4 (8.5)                  | 1 (7.7)                 | 5 (8.3)                |
|        |                       | Yes (+5)                  | 1 (2.1)                  | 0                       | 1 (1.7)                |
|        | Ablumin level         | >3.5 g/dL (+0)            | 5 (10.6)                 | 1 (7.7)                 | 6 (10.0)               |
|        |                       | <3.5 g/dL (+4)            | 0                        | 0                       | 0                      |
|        | Anorectal symptoms    | No (+0)                   | 5 (10.6)                 | 1 (7.7)                 | 6 (10.0)               |
|        |                       | Yes (+4)                  | 0                        | 0                       | 0                      |
|        | Anaemia               | No (+0)                   | 5 (10.6)                 | 1 (7.7)                 | 6 (10.0)               |
|        |                       | Yes (+4)                  | 0                        | 0                       | 0                      |
|        | Abdominal pain        | Less than daily (+0)      | 4 (8.5)                  | 1 (7.7)                 | 5 (8.3)                |
|        |                       | Daily (+3)                | 1 (2.1)                  | 0                       | 1 (1.7)                |
|        | Steroid use           | No (+0)                   | 3 (6.4)                  | 0                       | 3 (5.0)                |
|        |                       | Yes (+2)                  | 2 (4.3)                  | 1 (7.7)                 | 3 (5.0)                |
|        | Mucosal Lesions       | No (+0)                   | 6 (12.8)                 |                         | 6 (10.0)               |
|        |                       | Small (+6)                | 0                        |                         | 0                      |
|        |                       | Large or deep (+16)       | 0                        |                         | 0                      |
|        | Fistula               | No (+0)                   | 6 (12.8)                 |                         | 6 (10.0)               |
|        |                       | Yes (+11)                 | 0                        |                         | 0                      |
|        | Perianal abscess      | No (+0)                   | 6 (12.8)                 |                         | 6 (10.0)               |
|        |                       | Yes (+10)                 | 0                        |                         | 0                      |
|        | Intestinal resections | No (+0)                   | 6 (12.8)                 |                         | 6 (10.0)               |
|        |                       | <40 cm (+2)               | 0                        |                         | 0                      |
|        |                       | >=40 cm (+7)              | 0                        |                         | 0                      |

| Visit | Attribute              | Level                     | Hyrimoz<br>N=47<br>n (%) | Zessly<br>N=13<br>n (%) | Total<br>N=60<br>n (%) |
|-------|------------------------|---------------------------|--------------------------|-------------------------|------------------------|
|       | Stoma                  | No (+0)                   | 6 (12.8)                 |                         | 6 (10.0)               |
|       |                        | Yes (+11)                 | 0                        |                         | 0                      |
|       | Disease extent         | Limited disease (+0)      | 6 (12.8)                 |                         | 6 (10.0)               |
|       |                        | Extensive disease (+6)    | 0                        |                         | 0                      |
|       | Frequency loose stools | <10 per week (+0)         | 6 (12.8)                 |                         | 6 (10.0)               |
|       |                        | At least 10 per week (+6) | 0                        |                         | 0                      |
|       | Stricture              | No (+0)                   | 6 (12.8)                 |                         | 6 (10.0)               |
|       |                        | Yes (+5)                  | 0                        |                         | 0                      |
|       | CRP level              | 1-3 mg/L (+0)             | 4 (8.5)                  |                         | 4 (6.7)                |
|       |                        | 3-5 mg/L (+2)             | 1 (2.1)                  |                         | 1 (1.7)                |
|       |                        | above 5 mg/L (+5)         | 1 (2.1)                  |                         | 1 (1.7)                |
|       | Biologics use          | No (+0)                   | 2 (4.3)                  |                         | 2 (3.3)                |
|       |                        | Yes and improved (+2)     | 4 (8.5)                  |                         | 4 (6.7)                |
|       |                        | Yes but not improved (+5) | 0                        |                         | 0                      |
|       | Daily activity impact  | No (+0)                   | 6 (12.8)                 |                         | 6 (10.0)               |
|       |                        | Yes (+5)                  | 0                        |                         | 0                      |
|       | Ablumin level          | >3.5 g/dL (+0)            | 4 (8.5)                  |                         | 4 (6.7)                |
|       |                        | <3.5 g/dL (+4)            | 0                        |                         | 0                      |
|       | Anorectal symptoms     | No (+0)                   | 5 (10.6)                 |                         | 5 (8.3)                |
|       |                        | Yes (+4)                  | 1 (2.1)                  |                         | 1 (1.7)                |
|       | Anaemia                | No (+0)                   | 6 (12.8)                 |                         | 6 (10.0)               |
|       |                        | Yes (+4)                  | 0                        |                         | 0                      |
|       | Abdominal pain         | Less than daily (+0)      | 6 (12.8)                 |                         | 6 (10.0)               |
|       |                        | Daily (+3)                | 0                        |                         | 0                      |
|       | Steroid use            | No (+0)                   | 6 (12.8)                 |                         | 6 (10.0)               |
|       |                        | Yes (+2)                  | 0                        |                         | 0                      |

|              |                  |              | <b>Hyrimoz</b><br><b>N=47</b><br><b>n (%)</b> | <b>Zessly</b><br><b>N=13</b><br><b>n (%)</b> | <b>Total</b><br><b>N=60</b><br><b>n (%)</b> |
|--------------|------------------|--------------|---|--|---|
| <b>Visit</b> | <b>Attribute</b> | <b>Level</b> |   |  |   |

Percentages are based on total number per visit per treatment group in full analysis set.

**Summary of WPAI by visit (Full analysis set)**

| Visit      | Question  | Statistics | Hyrimoz<br>N=47 | Zessly<br>N=13 | Total<br>N=60 |
|------------|---|------------|-----------------|----------------|---------------|
| Enrollment | Q1. Currently employed -n (%)                         | Yes        | 11 (23.4)       | 2 (15.4)       | 13 (21.7)     |
|            |   | No         | 3 (6.4)         | 2 (15.4)       | 5 (8.3)       |
|            | Q2. Miss from work because of health problems (Hours) | n          | 11              | 2              | 13            |
|            |   | Mean       | 12.4            | 0.0            | 10.5          |
|            |   | SD         | 28.10           | 0.00           | 26.07         |
|            | Q3. Miss from work because of other reason (Hours)    | n          | 11              | 2              | 13            |
|            |   | Mean       | 7.8             | 0.0            | 6.6           |
|            |   | SD         | 13.85           | 0.00           | 12.98         |
|            | Q4. Actual work (Hours)                               | n          | 11              | 2              | 13            |
|            |   | Mean       | 19.0            | 22.0           | 19.5          |
|            |   | SD         | 21.01           | 25.46          | 20.57         |
|            | Q5. Health problem had effect on work                 | n          | 10              | 2              | 12            |
|            |   | Mean       | 3.0             | 0.5            | 2.6           |
|            |   | SD         | 3.02            | 0.71           | 2.91          |
|            | Q6. Health problem had effect on daily activities     | n          | 13              | 4              | 17            |
|            |   | Mean       | 5.1             | 3.0            | 4.6           |
|            |   | SD         | 3.25            | 3.56           | 3.34          |
| Week 8     | Q1. Currently employed -n (%)                         | Yes        | 13 (27.7)       |                | 13 (21.7)     |
|            |   | No         | 2 (4.3)         |                | 2 (3.3)       |
|            | Q2. Miss from work because of health problems (Hours) | n          | 13              |                | 13            |
|            |   | Mean       | 10.2            |                | 10.2          |
|            |   | SD         | 24.60           |                | 24.60         |
|            | Q3. Miss from work because of other reason (Hours)    | n          | 13              |                | 13            |
|            |   | Mean       | 8.3             |                | 8.3           |
|            |   | SD         | 23.69           |                | 23.69         |

| Visit   | Question  | Statistics | Hyrimoz<br>N=47 | Zessly<br>N=13 | Total<br>N=60 |
|---------|---|------------|-----------------|----------------|---------------|
| Week 14 | Q4. Actual work (Hours)                               | n          | 13              |                | 13            |
|         |   | Mean       | 24.7            |                | 24.7          |
|         |   | SD         | 16.25           |                | 16.25         |
|         | Q5. Health problem had effect on work                 | n          | 13              |                | 13            |
|         |   | Mean       | 2.2             |                | 2.2           |
|         |   | SD         | 2.94            |                | 2.94          |
|         | Q6. Health problem had effect on daily activities     | n          | 15              |                | 15            |
|         |   | Mean       | 2.0             |                | 2.0           |
|         |   | SD         | 2.80            |                | 2.80          |
|         | Q1. Currently employed -n (%)                         | Yes        |                 | 1 (7.7)        | 1 (1.7)       |
|         |   | No         |                 | 2 (15.4)       | 2 (3.3)       |
|         | Q2. Miss from work because of health problems (Hours) | n          |                 | 1              | 1             |
|         |   | Mean       |                 | 0.0            | 0.0           |
|         |   | SD         |                 |                |               |
|         | Q3. Miss from work because of other reason (Hours)    | n          |                 | 1              | 1             |
|         |   | Mean       |                 | 0.0            | 0.0           |
|         |   | SD         |                 |                |               |
|         | Q4. Actual work (Hours)                               | n          |                 | 1              | 1             |
|         |   | Mean       |                 | 40.0           | 40.0          |
|         |   | SD         |                 |                |               |
|         | Q5. Health problem had effect on work                 | n          |                 | 1              | 1             |
|         |   | Mean       |                 | 6.0            | 6.0           |
|         |   | SD         |                 |                |               |
|         | Q6. Health problem had effect on daily activities     | n          |                 | 3              | 3             |
|         |   | Mean       |                 | 2.7            | 2.7           |
|         |   | SD         |                 | 2.52           | 2.52          |



WPAI: Work productivity and activity impairment;  
The Q2-Q6 of WPAI are asked about the past 7 days.  
The score of health problem ranges from 0 to 10, and higher scores indicate having more problems.

**Summary of EQ-5D-5L by visit (EM1 analysis set)**

| Visit      | Dimension          | Description                    | Hyrimoz<br>N=38<br>n (%) | Zessly<br>N=12<br>n (%) | Total <sup>1</sup><br>N=50<br>n (%) |
|------------|--------------------|--------------------------------|--------------------------|-------------------------|-------------------------------------|
| Enrollment | Mobility           | 1 - No problem                 | 19 (50.0)                | 5 (41.7)                | 24 (48.0)                           |
|            |                    | 2 - Slight Problem             | 3 (7.9)                  | 0                       | 3 (6.0)                             |
|            |                    | 3 - Moderate Problem           | 3 (7.9)                  | 1 (8.3)                 | 4 (8.0)                             |
|            |                    | 4 - Severe Problem             | 0                        | 0                       | 0                                   |
|            |                    | 5 - Unable to/ extreme problem | 0                        | 0                       | 0                                   |
|            | Self-Care          | 1 - No problem                 | 23 (60.5)                | 6 (50.0)                | 29 (58.0)                           |
|            |                    | 2 - Slight Problem             | 2 (5.3)                  | 0                       | 2 (4.0)                             |
|            |                    | 3 - Moderate Problem           | 0                        | 0                       | 0                                   |
|            |                    | 4 - Severe Problem             | 0                        | 0                       | 0                                   |
|            |                    | 5 - Unable to/ extreme problem | 0                        | 0                       | 0                                   |
|            | Usual Activities   | 1 - No problem                 | 11 (28.9)                | 3 (25.0)                | 14 (28.0)                           |
|            |                    | 2 - Slight Problem             | 8 (21.1)                 | 0                       | 8 (16.0)                            |
|            |                    | 3 - Moderate Problem           | 4 (10.5)                 | 3 (25.0)                | 7 (14.0)                            |
|            |                    | 4 - Severe Problem             | 0                        | 0                       | 0                                   |
|            |                    | 5 - Unable to/ extreme problem | 2 (5.3)                  | 0                       | 2 (4.0)                             |
|            | Pain/Discomfort    | 1 - No problem                 | 2 (5.3)                  | 1 (8.3)                 | 3 (6.0)                             |
|            |                    | 2 - Slight Problem             | 17 (44.7)                | 0                       | 17 (34.0)                           |
|            |                    | 3 - Moderate Problem           | 4 (10.5)                 | 4 (33.3)                | 8 (16.0)                            |
|            |                    | 4 - Severe Problem             | 2 (5.3)                  | 1 (8.3)                 | 3 (6.0)                             |
|            |                    | 5 - Unable to/ extreme problem | 0                        | 0                       | 0                                   |
|            | Anxiety/Depression | 1 - No problem                 | 12 (31.6)                | 1 (8.3)                 | 13 (26.0)                           |

|        |                    |                                |           |          |           |
|--------|--------------------|--------------------------------|-----------|----------|-----------|
| Week 8 | Mobility           | 2 - Slight Problem             | 9 (23.7)  | 3 (25.0) | 12 (24.0) |
|        |                    | 3 - Moderate Problem           | 3 (7.9)   | 2 (16.7) | 5 (10.0)  |
|        |                    | 4 - Severe Problem             | 1 (2.6)   | 0        | 1 (2.0)   |
|        |                    | 5 - Unable to/ extreme problem | 0         | 0        | 0         |
|        |                    | 1 - No problem                 | 13 (34.2) |          | 13 (26.0) |
|        | Self-Care          | 2 - Slight Problem             | 4 (10.5)  |          | 4 (8.0)   |
|        |                    | 3 - Moderate Problem           | 0         |          | 0         |
|        |                    | 4 - Severe Problem             | 0         |          | 0         |
|        |                    | 5 - Unable to/ extreme problem | 0         |          | 0         |
|        |                    | 1 - No problem                 | 15 (39.5) |          | 15 (30.0) |
|        | Usual Activities   | 2 - Slight Problem             | 2 (5.3)   |          | 2 (4.0)   |
|        |                    | 3 - Moderate Problem           | 0         |          | 0         |
|        |                    | 4 - Severe Problem             | 0         |          | 0         |
|        |                    | 5 - Unable to/ extreme problem | 0         |          | 0         |
|        |                    | 1 - No problem                 | 11 (28.9) |          | 11 (22.0) |
|        | Pain/Discomfort    | 2 - Slight Problem             | 3 (7.9)   |          | 3 (6.0)   |
|        |                    | 3 - Moderate Problem           | 3 (7.9)   |          | 3 (6.0)   |
|        |                    | 4 - Severe Problem             | 0         |          | 0         |
|        |                    | 5 - Unable to/ extreme problem | 0         |          | 0         |
|        |                    | 1 - No problem                 | 5 (13.2)  |          | 5 (10.0)  |
|        | Anxiety/Depression | 2 - Slight Problem             | 8 (21.1)  |          | 8 (16.0)  |
|        |                    | 3 - Moderate Problem           | 4 (10.5)  |          | 4 (8.0)   |
|        |                    | 4 - Severe Problem             | 0         |          | 0         |
|        |                    | 5 - Unable to/ extreme problem | 0         |          | 0         |
|        |                    | 1 - No problem                 | 9 (23.7)  |          | 9 (18.0)  |
|        |                    | 2 - Slight Problem             | 6 (15.8)  |          | 6 (12.0)  |
|        |                    | 3 - Moderate Problem           | 1 (2.6)   |          | 1 (2.0)   |
|        |                    | 4 - Severe Problem             | 1 (2.6)   |          | 1 (2.0)   |

|         |                    |                                |   |          |         |
|---------|--------------------|--------------------------------|---|----------|---------|
| Week 14 | Mobility           | 5 - Unable to/ extreme problem | 0 |          | 0       |
|         |                    | 1 - No problem                 |   | 3 (25.0) | 3 (6.0) |
|         |                    | 2 - Slight Problem             |   | 0        | 0       |
|         |                    | 3 - Moderate Problem           |   | 0        | 0       |
|         |                    | 4 - Severe Problem             |   | 0        | 0       |
|         | Self-Care          | 5 - Unable to/ extreme problem |   | 0        | 0       |
|         |                    | 1 - No problem                 |   | 3 (25.0) | 3 (6.0) |
|         |                    | 2 - Slight Problem             |   | 0        | 0       |
|         |                    | 3 - Moderate Problem           |   | 0        | 0       |
|         |                    | 4 - Severe Problem             |   | 0        | 0       |
|         | Usual Activities   | 5 - Unable to/ extreme problem |   | 0        | 0       |
|         |                    | 1 - No problem                 |   | 2 (16.7) | 2 (4.0) |
|         |                    | 2 - Slight Problem             |   | 1 (8.3)  | 1 (2.0) |
|         |                    | 3 - Moderate Problem           |   | 0        | 0       |
|         |                    | 4 - Severe Problem             |   | 0        | 0       |
|         | Pain/Discomfort    | 5 - Unable to/ extreme problem |   | 0        | 0       |
|         |                    | 1 - No problem                 |   | 1 (8.3)  | 1 (2.0) |
|         |                    | 2 - Slight Problem             |   | 1 (8.3)  | 1 (2.0) |
|         |                    | 3 - Moderate Problem           |   | 1 (8.3)  | 1 (2.0) |
|         |                    | 4 - Severe Problem             |   | 0        | 0       |
|         | Anxiety/Depression | 5 - Unable to/ extreme problem |   | 0        | 0       |
|         |                    | 1 - No problem                 |   | 1 (8.3)  | 1 (2.0) |
|         |                    | 2 - Slight Problem             |   | 2 (16.7) | 2 (4.0) |
|         |                    | 3 - Moderate Problem           |   | 0        | 0       |
|         |                    | 4 - Severe Problem             |   | 0        | 0       |
|         |                    | 5 - Unable to/ extreme problem |   | 0        | 0       |

| Visit | Question | Statistics | Hyrimoz<br>N=47 | Zessly<br>N=13 | Total<br>N=60 |
|-------|----------|------------|-----------------|----------------|---------------|
|-------|----------|------------|-----------------|----------------|---------------|

Percentages are based on total number per visit per treatment group in EM1 analysis set.

4 Subjects who treated with Zessly used EQ-5D-5L with 3-scale were excluded in the analysis and were coded as protocol deviation.

<sup>1</sup>The questionnaire was voluntary. Only 50 patients filled the questionnaire.

**Summary of SF-MPQ by visit (EM1 analysis set)**

| <b>Visit</b> | <b>Dimension</b> | <b>Description</b> | <b>Hyrimoz<br/>N=38<sup>1</sup><br/>n (%)</b> |
|--------------|------------------|--------------------|---|
| Enrollment   | Throbbing        | 0-None             | 10 (26.3)                                     |
|              |                  | 1-Mild             | 1 (2.6)                                       |
|              |                  | 2-Moderate         | 1 (2.6)                                       |
|              |                  | 3-Severe           | 0   |
|              | Shooting         | 0-None             | 8 (21.1)                                      |
|              |                  | 1-Mild             | 1 (2.6)                                       |
|              |                  | 2-Moderate         | 2 (5.3)                                       |
|              |                  | 3-Severe           | 1 (2.6)                                       |
|              | Stabbing         | 0-None             | 5 (13.2)                                      |
|              |                  | 1-Mild             | 3 (7.9)                                       |
|              |                  | 2-Moderate         | 3 (7.9)                                       |
|              |                  | 3-Severe           | 1 (2.6)                                       |
|              | Sharp            | 0-None             | 9 (23.7)                                      |
|              |                  | 1-Mild             | 3 (7.9)                                       |
|              |                  | 2-Moderate         | 0   |
|              |                  | 3-Severe           | 0   |
|              | Cramping         | 0-None             | 7 (18.4)                                      |
|              |                  | 1-Mild             | 4 (10.5)                                      |
|              |                  | 2-Moderate         | 0   |
|              |                  | 3-Severe           | 1 (2.6)                                       |
|              | Gnawing          | 0-None             | 9 (23.7)                                      |
|              |                  | 1-Mild             | 2 (5.3)                                       |
|              |                  | 2-Moderate         | 1 (2.6)                                       |
|              |                  | 3-Severe           | 0   |
|              | Hot-burning      | 0-None             | 8 (21.1)                                      |

| Visit | Dimension         | Description | Hyrimoz<br>N=38 <sup>1</sup><br>n (%) |
|-------|-------------------|-------------|---------------------------------------|
|       |                   | 1-Mild      | 2 (5.3)                               |
|       |                   | 2-Moderate  | 2 (5.3)                               |
|       |                   | 3-Severe    | 0                                     |
|       | Aching            | 0-None      | 7 (18.4)                              |
|       |                   | 1-Mild      | 3 (7.9)                               |
|       |                   | 2-Moderate  | 2 (5.3)                               |
|       |                   | 3-Severe    | 0                                     |
|       | Heavy             | 0-None      | 6 (15.8)                              |
|       |                   | 1-Mild      | 2 (5.3)                               |
|       |                   | 2-Moderate  | 4 (10.5)                              |
|       |                   | 3-Severe    | 0                                     |
|       | Tender            | 0-None      | 8 (21.1)                              |
|       |                   | 1-Mild      | 2 (5.3)                               |
|       |                   | 2-Moderate  | 2 (5.3)                               |
|       |                   | 3-Severe    | 0                                     |
|       | Splitting         | 0-None      | 11 (28.9)                             |
|       |                   | 1-Mild      | 1 (2.6)                               |
|       |                   | 2-Moderate  | 0                                     |
|       |                   | 3-Severe    | 0                                     |
|       | Tiring-exhausting | 0-None      | 5 (13.2)                              |
|       |                   | 1-Mild      | 4 (10.5)                              |
|       |                   | 2-Moderate  | 3 (7.9)                               |
|       |                   | 3-Severe    | 0                                     |
|       | Sickening         | 0-None      | 8 (21.1)                              |
|       |                   | 1-Mild      | 3 (7.9)                               |
|       |                   | 2-Moderate  | 1 (2.6)                               |

|              |                        |                    | <b>Hyrimoz<br/>N=38<sup>1</sup><br/>n (%)</b> |
|--------------|------------------------|--------------------|---|
| <b>Visit</b> | <b>Dimension</b>       | <b>Description</b> |   |
| Week 8       | Fearful                | 3-Severe           | 0   |
|              |                        | 0-None             | 10 (26.3)                                     |
|              |                        | 1-Mild             | 2 (5.3)                                       |
|              |                        | 2-Moderate         | 0   |
|              | Punishing-cruel        | 3-Severe           | 0   |
|              |                        | 0-None             | 11 (28.9)                                     |
|              |                        | 1-Mild             | 0   |
|              |                        | 2-Moderate         | 1 (2.6)                                       |
|              | Present Pain Intensity | 3-Severe           | 0   |
|              |                        | 0-No Pain          | 2 (5.3)                                       |
|              |                        | 1-Mild             | 4 (10.5)                                      |
|              |                        | 2-Discomforting    | 1 (2.6)                                       |
|              |                        | 3-Distressing      | 0   |
|              |                        | 4-Horrible         | 0   |
|              |                        | 5-Excruciating     | 1 (2.6)                                       |
|              | Throbbing              | 0-None             | 10 (26.3)                                     |
|              |                        | 1-Mild             | 1 (2.6)                                       |
|              |                        | 2-Moderate         | 1 (2.6)                                       |
|              |                        | 3-Severe           | 0   |
|              | Shooting               | 0-None             | 11 (28.9)                                     |
|              |                        | 1-Mild             | 1 (2.6)                                       |
|              |                        | 2-Moderate         | 0   |
|              |                        | 3-Severe           | 0   |
|              | Stabbing               | 0-None             | 8 (21.1)                                      |
|              |                        | 1-Mild             | 3 (7.9)                                       |
|              |                        | 2-Moderate         | 0   |

|              |                  |                    | <b>Hyrimoz<br/>N=38<sup>1</sup><br/>n (%)</b> |
|--------------|------------------|--------------------|---|
| <b>Visit</b> | <b>Dimension</b> | <b>Description</b> |   |
|              | Sharp            | 3-Severe           | 1 (2.6)                                       |
|              |                  | 0-None             | 10 (26.3)                                     |
|              |                  | 1-Mild             | 1 (2.6)                                       |
|              |                  | 2-Moderate         | 0   |
|              | Cramping         | 3-Severe           | 1 (2.6)                                       |
|              |                  | 0-None             | 7 (18.4)                                      |
|              |                  | 1-Mild             | 4 (10.5)                                      |
|              |                  | 2-Moderate         | 1 (2.6)                                       |
|              | Gnawing          | 3-Severe           | 0   |
|              |                  | 0-None             | 11 (28.9)                                     |
|              |                  | 1-Mild             | 0   |
|              |                  | 2-Moderate         | 1 (2.6)                                       |
|              | Hot-burning      | 3-Severe           | 0   |
|              |                  | 0-None             | 8 (21.1)                                      |
|              |                  | 1-Mild             | 1 (2.6)                                       |
|              |                  | 2-Moderate         | 2 (5.3)                                       |
|              | Aching           | 3-Severe           | 1 (2.6)                                       |
|              |                  | 0-None             | 7 (18.4)                                      |
|              |                  | 1-Mild             | 4 (10.5)                                      |
|              |                  | 2-Moderate         | 0   |
|              | Heavy            | 3-Severe           | 1 (2.6)                                       |
|              |                  | 0-None             | 7 (18.4)                                      |
|              |                  | 1-Mild             | 4 (10.5)                                      |
|              |                  | 2-Moderate         | 0   |
|              | Tender           | 3-Severe           | 1 (2.6)                                       |
|              |                  | 0-None             | 7 (18.4)                                      |



| Visit | Dimension              | Description     | Hyrimoz<br>N=38 <sup>1</sup><br>n (%) |
|-------|------------------------|-----------------|---------------------------------------|
|       |                        | 1-Mild          | 3 (7.9)                               |
|       |                        | 2-Moderate      | 2 (5.3)                               |
|       |                        | 3-Severe        | 0                                     |
|       | Splitting              | 0-None          | 10 (26.3)                             |
|       |                        | 1-Mild          | 2 (5.3)                               |
|       |                        | 2-Moderate      | 0                                     |
|       |                        | 3-Severe        | 0                                     |
|       | Tiring-exhausting      | 0-None          | 8 (21.1)                              |
|       |                        | 1-Mild          | 2 (5.3)                               |
|       |                        | 2-Moderate      | 2 (5.3)                               |
|       |                        | 3-Severe        | 0                                     |
|       | Sickening              | 0-None          | 10 (26.3)                             |
|       |                        | 1-Mild          | 1 (2.6)                               |
|       |                        | 2-Moderate      | 1 (2.6)                               |
|       |                        | 3-Severe        | 0                                     |
|       | Fearful                | 0-None          | 10 (26.3)                             |
|       |                        | 1-Mild          | 0                                     |
|       |                        | 2-Moderate      | 2 (5.3)                               |
|       |                        | 3-Severe        | 0                                     |
|       | Punishing-cruel        | 0-None          | 12 (31.6)                             |
|       |                        | 1-Mild          | 0                                     |
|       |                        | 2-Moderate      | 0                                     |
|       |                        | 3-Severe        | 0                                     |
|       | Present Pain Intensity | 0-No Pain       | 4 (10.5)                              |
|       |                        | 1-Mild          | 2 (5.3)                               |
|       |                        | 2-Discomforting | 0                                     |

|              |                  |                    | <b>Hyrimoz<br/>N=38<sup>1</sup><br/>n (%)</b> |
|--------------|------------------|--------------------|---|
| <b>Visit</b> | <b>Dimension</b> | <b>Description</b> |   |
|              |                  | 3-Distressing      | 0   |
|              |                  | 4-Horrible         | 2 (5.3)                                       |
|              |                  | 5-Excruciating     | 0   |

Percentages are based on total number per visit per treatment group in EM1 analysis set.

<sup>1</sup> SF-MPQ relates to injection site pain and therefore is not applicable to Zessly recipients. The questionnaire was voluntary and therefore not all Hyrimoz-treated patients provided data.

## Safety Results

### Overall treatment emergent adverse events (Safety analysis set)

|  | <b>Hyrimoz<br/>N=47<br/>n (%)</b> | <b>Zessly<br/>N=13<br/>n (%)</b> | <b>Total<br/>N=60<br/>n (%)</b> |
|--|-----------------------------------|----------------------------------|---------------------------------|
| Number of patients with at least one TEAE                          | 18 (38.3)                         | 3 (23.1)                         | 21 (35.0)                       |
| Number of patients with at least one severe TEAE                   | 2 (4.3)                           | 0                                | 2 (3.3)                         |
| Number of patients with at least one SAE                           | 4 (8.5)                           | 0                                | 4 (6.7)                         |
| Number of patients with at least one treatment related TEAE        | 7 (14.9)                          | 1 (7.7)                          | 8 (13.3)                        |
| Number of patients with at least one treatment related SAE         | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Number of patients with AEs of special interest <sup>1†</sup>      | 5 (10.6)                          | 0                                | 5 (8.3)                         |
| Number of patients with TEAEs leading to treatment discontinuation | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Number of patients with TEAEs leading to hospitalization           | 4 (8.5)                           | 0                                | 4 (6.7)                         |
| Number of deaths   | 0                                 | 0                                | 0                               |

<sup>1</sup> AESI reported during the study did not fulfill the pre-specified criteria as per protocol and were thus incorrectly reported by the investigators.

Percentages are based on total number per group in safety analysis set.

Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category.

Patients with events in more than 1 category are counted once in each of those categories.

**Serious treatment emergent adverse events, by primary system organ class and preferred term (Safety analysis set)**

| <b>Primary system organ class<br/>Preferred term</b> | <b>Hyrimoz<br/>N=47<br/>n (%)</b> | <b>Zessly<br/>N=13<br/>n (%)</b> | <b>Total<br/>N=60<br/>n (%)</b> |
|--|-----------------------------------|----------------------------------|---------------------------------|
| Number of patients with at least one serious TEAE    | 4 (8.5)                           | 0                                | 4 (6.7)                         |
| Gastrointestinal disorders                           | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Abdominal pain                                       | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Ileal stenosis                                       | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Infections and infestations                          | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Cytomegalovirus colitis                              | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Musculoskeletal and connective tissue disorders      | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Fistula  | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Vascular disorders                                   | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Aortic stenosis                                      | 1 (2.1)                           | 0                                | 1 (1.7)                         |

Percentages are based on total number per group in safety analysis set.

A subject with multiple adverse events within a primary SOC is counted only once in the total row.

A subject with multiple occurrences of an AE under 1 treatment is counted only once in this AE category for that treatment.

MedDRA Version 23.0 has been used for the reporting of AEs

**Adverse Events by System Organ Class**

| <b>Primary system organ class</b>                    | <b>Hyrimoz<br/>N=47<br/>n (%)</b> | <b>Zessly<br/>N=13<br/>n (%)</b> | <b>Total<br/>N=60<br/>n (%)</b> |
|--|-----------------------------------|----------------------------------|---------------------------------|
| Number of patients with at least one TEAE            | 18 (38.3)                         | 3 (23.1)                         | 21 (35.0)                       |
| Gastrointestinal disorders                           | 6 (12.8)                          | 1 (7.7)                          | 7 (11.7)                        |
| Infections and infestations                          | 5 (10.6)                          | 1 (7.7)                          | 6 (10.0)                        |
| Musculoskeletal and connective tissue disorders      | 4 (8.5)                           | 0                                | 4 (6.7)                         |
| Skin and subcutaneous tissue disorders               | 3 (6.4)                           | 1 (7.7)                          | 4 (6.7)                         |
| General disorders and administration site conditions | 3 (6.4)                           | 0                                | 3 (5.0)                         |
| Investigations                                       | 3 (6.4)                           | 0                                | 3 (5.0)                         |
| Nervous system disorders                             | 2 (4.3)                           | 0                                | 2 (3.3)                         |
| Eye disorders  | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Respiratory, thoracic and mediastinal disorders      | 0                                 | 1 (7.7)                          | 1 (1.7)                         |
| Vascular disorders                                   | 1 (2.1)                           | 0                                | 1 (1.7)                         |

Percentages are based on total number per group in safety analysis set.

A subject with multiple adverse events within a primary system organ class is counted only once in the total row.

A subject with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment.

MedDRA Version 23.0 has been used for the reporting of adverse events.

**Most Frequently Reported AEs Overall by Preferred Term n (%)**

| <b>Preferred term</b>                     | <b>Hyrimoz<br/>N=47<br/>n (%)</b> | <b>Zessly<br/>N=13<br/>n (%)</b> | <b>Total<br/>N=60<br/>n (%)</b> |
|---|-----------------------------------|----------------------------------|---------------------------------|
| Number of patients with at least one TEAE | 18 (38.3)                         | 3 (23.1)                         | 21 (35.0)                       |
| Abdominal pain                            | 3 (6.4)                           | 0                                | 3 (5.0)                         |
| Diarrhoea                                 | 2 (4.3)                           | 0                                | 2 (3.3)                         |
| Oral herpes                               | 2 (4.3)                           | 0                                | 2 (3.3)                         |
| Pruritus                                  | 2 (4.3)                           | 0                                | 2 (3.3)                         |
| Influenza like illness                    | 2 (4.3)                           | 0                                | 2 (3.3)                         |
| Faecal calprotectin increased             | 2 (4.3)                           | 0                                | 2 (3.3)                         |
| Headache                                  | 2 (4.3)                           | 0                                | 2 (3.3)                         |
| Abdominal pain upper                      | 0                                 | 1 (7.7)                          | 1 (1.7)                         |
| Enterocutaneous fistula                   | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Gastrooesophageal reflux disease          | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Ileal stenosis                            | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| COVID-19                                  | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Cytomegalovirus colitis                   | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Herpes zoster                             | 0                                 | 1 (7.7)                          | 1 (1.7)                         |
| Infection susceptibility increased        | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Influenza                                 | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Arthralgia                                | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Fistula                                   | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Growing pains                             | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Intervertebral disc protrusion            | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Dry skin                                  | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Skin fissures                             | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Urticaria                                 | 0                                 | 1 (7.7)                          | 1 (1.7)                         |

| <b>Preferred term</b>        | <b>Hyrimoz<br/>N=47<br/>n (%)</b> | <b>Zessly<br/>N=13<br/>n (%)</b> | <b>Total<br/>N=60<br/>n (%)</b> |
|------------------------------|-----------------------------------|----------------------------------|---------------------------------|
| Pain                         | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Pyrexia                      | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| C-reactive protein increased | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Haemoglobin decreased        | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Eye inflammation             | 1 (2.1)                           | 0                                | 1 (1.7)                         |
| Tonsillar hypertrophy        | 0                                 | 1 (7.7)                          | 1 (1.7)                         |
| Aortic stenosis              | 1 (2.1)                           | 0                                | 1 (1.7)                         |

Percentages are based on total number per group in safety analysis set.

A subject with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment.

MedDRA Version 23.0 has been used for the reporting of adverse events.

**Conclusion:**

The early termination of the study led to a restricted sample size, with a reduced number of patients in the Hyrimoz group, a lower number of patients in the Zessly group, and a large difference in size between both groups, which strongly limits the interpretation of the results obtained.

The safety profile was as expected, with events consistent with those to be expected in CD patients. Hyrimoz and Zessly were generally safe and well tolerated. No deaths occurred during the study.

**Date of Clinical Study Report**

11 November 2020