CLINICAL INVESTIGATION REPORT SYNOPSIS: PMCF STUDY DV0005

Name of company: UCB Pharma	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: CZP ava device	**Volume**: Not applicable	
Name of active ingredient: Certolizumab pegol	**Page:** Not applicable	

Title of study:

A multicenter, observational post-market clinical follow-up study in patients with RA, PsA, or axSpA assessing the patient experience with the Cimzia ava device or other TNF-blocker auto-injector devices

Study Number: DV0005

Investigator(s): 31 investigators in 4 European countries documented patient data.

Study site(s): DV0005 was a multicenter study; a total of 31 active study sites enrolled patients for evaluation data (9 in Belgium, 7 in Germany, 6 in Italy, and 9 in Spain).

Publication(s) (reference[s]): None.

Observational period: 3 years; about 9 months per patient **First patient observational point (OP) 1:** 15 Nov 2018 **Last patient OP3:** 03 Nov 2021	**Phase of development:** Post-market clinical follow-up of device

Objective(s):

The primary objective of this PMCF device study was to assess the patients' satisfaction with self-injection by either ava or other auto-injector devices for administration of a TNF-blocking agent at OP1 using 6 questions of the post-SIAQ V2.1 satisfaction domain.

Secondary objective was to assess the persistence of use of ava and other auto-injector devices for administration of a TNF-blocking agent at about 12 months (360 days) after device prescription by evaluation of the time to discontinuation.

Other objectives comprise assessment of the persistence of use of ava and other auto-injector devices for administration of a TNF-blocking agent at about 180 days after device prescription by evaluation of time to discontinuation; evaluation of the percentage of patients with persistent use of ava or other auto-injector devices for administration of a TNF-blocking agent at about 180 and 360 days after device prescription; collection of further information on the patients' experience of self-injection by either ava or other auto-injector devices for administration of a TNF-blocking agent at OP1 using post-SIAQ V2.1 additional domains and a specific CZP ava device questionnaire; evaluation of patients' compliance on the use of ava or other auto-injector devices for the administration of a TNF-blocking

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agent at OP2 and OP3 using the patients' self-reported drug administration logs; evaluation of patients' compliance on the use of ava at OP2 and OP3 considering the internal ava injection log; evaluation of the physician's prescription decision for all drug-device combinations described at OP1 per patient (ie, ava or other auto-injector devices for administration of TNF-blocking agents); evaluation of the physician's assessment of utility of the ava injection log data at OP3 per patient; evaluation of the patient-assessed clinical outcome at OP1, OP2, and OP3; assessment of safety and tolerability of the ava device.

Methodology:

DV0005 was an exploratory multicenter PMCF device study evaluating the use of the Cimzia® ava device (ava) for administration of certolizumab pegol (CZP) and other auto-injector devices for administration of different tumor necrosis factor (TNF)-blocking agents in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or axial spondyloarthritis (axSpA). Patients who had already been using their previously prescribed auto-injector devices for administration of TNF-blockers (ava or other) for about 3 months were selected by the sites. No additional diagnostic or therapeutic procedures were applied. The choice of medical treatment was at the discretion of the treating physician, and had to have been made independently by the treating physician during routine clinical practice about 3 months prior to study start. Thus, patients were expected to be already familiar with their respective device at study start. Patients were followed as per current clinical practice for their condition. Three observational points (OPs) had been defined for data collection spanning about 9 months of treatment of the individual patient: **OP1** (Day 1) at about 3 months after prescription and first auto-injector administration of the respective TNF-blocking agent, **OP2** at about 3 months after OP1, and **OP3** at about 6 months after OP2.

Number of subjects (planned and analyzed):

It was planned that study sites in approximately 10 European countries should document data of a total number of about 200 patients with about 100 patients using the CZP ava device and about 100 patients using other devices over a period of about 2 years after study approval.

Eventually, data from 184 patients were collected and documented in the database by 31 active study sites in Spain, Belgium, Italy, and Germany. 77 patients using ava and 101 patients using other devices were included in the enrolled analysis set of patients (ES). Thereof, a deviation regarding selection criteria was seen in 21 patients, overall: 10 patients using ava and 11 patients using other devices. No further data were collected for 6 patients considered selection failures.

Diagnosis and main criteria for inclusion:

Before any data were collected for any patient in this observational PMCF device study, written data consent was collected and properly documented.

The following selection criteria had to be followed for patients entering the study:

1. Adult patient (aged ≥18 years) diagnosed with RA, PsA, or axSpA

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2. Patient started using ava with CZP or another auto-injector device for administration of TNF-blocking agents (except CZP) about 3 months prior to OP1
3. A Patient Data Consent Form signed and dated by the patient prior to any study data collection

No withdrawal criteria were defined for this PMCF device study.

Test products: Cimzia® ava device and other auto-injector devices for administration of a TNF-blocking agent as prescribed by the treating physician

Dose(s): According to routine prescription

Mode of administration: Subcutaneous self-injection

Batch number(s): Not applicable

Duration of treatment: Not applicable

Reference therapy, dose(s) and mode of administration, batch number(s): Not applicable

Criteria for evaluation:

- Primary variable: Summary score describing patient's satisfaction with self-injection as calculated from 6 questions (Q15, and Q17 to Q21) of the post-SIAQ V2.1 satisfaction domain documented about 3 months (OP1) after device prescription.
- Secondary variable: Time in days from initial prescription to discontinuation of device use at about 12 months (360 days) after device prescription (persistence of use).

Other variables

- Persistence of use:
  - Time in days from initial prescription to discontinuation of device use at about 180 days after device prescription
  - Number and percentage of patients with persistent device use at about 180 and 360 days after device prescription
- Patients' self-injection experience:
  - Summary scores of post-SIAQ V2.1 additional domains describing feelings about injections, self-image, self-confidence, pain, skin reaction, and ease of use documented at OP1
  - Summary scores of CZP ava device questionnaire results recorded at OP1 for patients using ava
- Patients' compliance:
  - Number of doses actually injected according to the patient's drug administration log vs number of doses expected from physician's prescription, both at OP2 and OP3
  - Number of doses actually injected according to CZP ava device injection log data vs number of doses expected from physician's prescription, at OP2, and OP3 for patients using ava
- Physicians' perspectives:

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- Summary documentation of reasons for the physician's prescription decision at OP1 per patient
- Score of the verbal rating scale (VRS; Likert Scale) of the physician's assessment on utility of the ava injection log data at OP3 for patients using ava
- Summary documentation of the physician's use of the ava injection log data at OP3 per patient

- Clinical outcome: HAQ score at OP1, OP2 and OP3.
- Safety (patients using CZP ava device, only)
  - Adverse events, serious and non-serious ([S]AEs)
  - Adverse drug reactions, serious and non-serious ([S]ADRs)
  - Adverse device effects, serious and non-serious ([S]ADEs) and device deficiencies (DDs)

Statistical methods:

Statistical analyses were provided according to the detailed description in the Statistical Analysis Plan (SAP).

The statistical analysis and generation of tables, figures, patient data listings, and statistical output were performed by acromion GmbH using SAS Version 9.4. All statistical analyses were exploratory and done according to the principle 'as observed', ie, missing values were not replaced. Patients' disposition was based on the ES including all patients who signed data consent. All analysis of effectiveness were performed using the FAS consisting of all patients of the ES with valid data for the primary outcome variable. Safety variables were presented for patients of the ES using the ava device at least once on or after OP1.

All available data were included in the analyses and summarized as far as possible. In general, no substitution of missing data was done, ie, missing data were not replaced but were handled as 'missing' in the statistical evaluation. Partial dates were imputed for statistical analyses for specific outcomes. The specific imputation rules were provided in the SAP. However, as a global convention, imputed dates were not to be shown in patient data listings.

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Study periods were the pre-observational periods covering about 3 months before the date of OP1, and the observational period from the date of OP1 until the date of OP3 (for patients completing the observational period) or until the date of premature study termination (for patients who discontinued during the observational period).

Descriptive statistics are displayed to provide an overview of the study results. For categorical variables, the number and percentage of patients in each category are presented. The denominator for percentages is based on the number of patients appropriate for the purpose of analysis. All percentages are displayed to one decimal place. For continuous variables, descriptive statistics include number of patients with available measurements (n), mean, standard deviation (SD), median, minimum, and maximum. Time-to-event variables are summarized by Kaplan-Meier analyses.

Summary and conclusions:

Subject disposition: 184 patients were enrolled including 6 selection failures: One patient had not started device use within the allowed time prior to OP1 (start of use <2 or >5 months before OP1); one patient did not use a TNF-blocking agent; three patients were not treated with an auto-injector device, and one patient stopped use of the ava device before OP1. The enrolled set (ES) consists of 77 patients using the ava device and 101 patients using other devices.

Important protocol deviations were observed in 10/77 patients using ava and 11/101 patients using other devices. Deviations mostly refer to time between first prescription of drug/device combination and OP1 (<2 or >5 months). One patient using other devices who had not completed the post-SIAQ at OP1 in person was excluded from the full analysis set (FAS) because of procedural non-compliance. Thus, the FAS comprises 77/77 patients using ava (100%) and 100/101 patients using other devices (99.0%).

Demographics: Patients using ava were mean 41.5 years old (SD=11.6, median=39 years; 63.3% of patients aged 18 to 44 years), patients using other devices were mean 51.3 years old (SD=13.5, median=50 years; 36.6% of patients aged 18 to 44 years and 42.6% aged 45 to 64 years). 79.2% of patients using ava were women. In the group of patients using other devices sex ratio was balanced. 40.3% of patients using ava and 32.7% of patients using other devices had rheumatoid arthritis as underlying disease; 16.9% of patients using ava and 22.8% of patients using other devices had psoriatic arthritis. Previous use of an auto-injector device was reported for 41.6% of patients using ava and 34.7% of patients using other devices: this comprises use of an autoinjector device for any indication. Previous use of an auto-injector device for the underlying disease was reported for 56.3% of patients using ava and 71.4% of patients using other devices. The majority of patients in the latter group used biosimilars (80.2%).

Effectiveness: Primary outcome variable was the summary score of satisfaction with self-infection as captured by the post-SIAQ V2.1 modified satisfaction domain after three months of device use, i.e., at OP1. Overall, satisfaction according to this summary score was high in both groups (see table). Post-hoc subgroup analyses male patients scored numerically higher than female patients in both groups, as

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did patients aged 18 to 44 years in the ava device group. Many of the subgroups, however, are small and results should be interpreted with caution.

	CZP ava, N=77 (full analysis set)	**Other devices, N=100** (full analysis set)
n patients with answers	77	100
Satisfaction with self-injection		
Mean (SD); median	7.976 (1.485); 7.917	8.192 (1.547); 8.333
95% CI	7.639 to 8.313	7.885 to 8.499
Satisfaction with self-injection adjusted for gender and age		
LS Mean (SE)	8.100 (0.192)	8.215 (0.154)
95% CI	7.721 to 8.478	7.910 to 8.520
SD=standard deviation, SE=standard error, CI=confidence interval; data source: Tables 3.1.1.1 and 3.1.1.5		

In both device groups, the majority of patients were still using their device at 12 months: 66.2% of patients using ava and 78.0% of patients using other devices. Retention rate declined to 90% after 3.8 months in patients using ava and 6.1 months in patients using other devices.

Patients using ava in this study had a mean score of 7.600 (SD=1.748, median 7.813) in the post-SIAQ additional domain 'pain and skin reactions', patients using other devices had a mean score of 8.841 (SD=1.171, median 9.063; higher scores mean less fear / anxiety). This may imply that ava patients may have been more afraid of needles or injections and may have experienced more pain and discomfort by self-injections.

Satisfaction with ava device functionality has been captured using the CZP ava device questionnaire. Nearly all patients reported controlling of injection speed, pausing or stopping when giving themselves an injection, and remembering to take the next injection as "easy" or "very easy". Patients accordingly were "satisfied" (42.9%) or "very satisfied" (50.9%) with the control of injection. Median summary score for this endpoint was 8.88.

Compliance was high in both groups (mean, median and 95% CI >80%); median percentage of doses administered was 100% in patients using other devices (both, at OP2 and OP3) and 88.2% in patients using ava at OP2 and 92.9% at OP3, according to the drug administration log.

The majority of prescription decisions were based on the TNF-blocker, and most prescriptions were done according to clinical guidelines/local standard of care. The combination of drug and device led physicians' decision in 26.0% of cases in the ava group compared to 16.0% in the group of patients using other devices.

Physicians reported for the majority of patients at OP3 that the ava internal injection log was quite or very useful, overall, and quite or very useful for checking compliance. Physicians of ava patients discontinuing before OP3 did not complete this questionnaire which accounts for 26.0% of 'missing' answers.

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Patients of both groups had comparatively low HAQ-DI scores at OP1 (mean=0.7110, SD=0.6323 in patients of the ava group and 0.6725, SD=0.6338 in patients using other devices). Degree of disability thus was low, overall. No relevant changes were recorded for OP2 and OP3. Mean disease-related pain according to the VAS score was similar in both groups.

Pharmacokinetics/pharmacodynamics results: Not applicable.

Safety:

TEAEs were most frequently reported in the SOCs 'general disorders and administration site conditions' (mostly HLT 'injection site reactions') and 'infections and infestations' (mostly HLT 'upper respiratory tract infections'), followed by 'nervous system disorders', and 'skin and subcutaneous tissue disorders' (see table). This pattern of SOC and HLT frequency is in-line with the established safety profile of CZP. No new safety signals were identified for CZP.

TEAEs occurring in ≥2 patients: **MedDRA 22.0—SOC, HLT**	**CZP ava, N=77** (safety set) n (%), n events
Any TEAE	36 (46.8), 73
General disorders and administration site conditions	22 (28.6), 35
Injection site reactions	19 (24.7), 29
Administration site reactions NEC	2 (2.6), 2
Febrile disorders	2 (2.6), 2
Infections and infestations	13 (16.9), 17
Upper respiratory tract infections	5 (6.5), 6
Influenza viral infections	2 (2.6), 3
Urinary tract infections	2 (2.6), 3
Nervous system disorders	5 (6.5), 8
Headaches NEC	2 (2.6), 5
Skin and subcutaneous system disorders	3 (3.9), 3
Psychiatric disorders	2 (2.6), 2
Renal and urinary disorders	2 (2.6), 2
Urinary tract signs and symptoms NEC	2 (2.6), 2

Six patients (7.8%) discontinued the study because of TEAEs, mostly injection site reactions. 24.7% of patients (19/77) experienced drug-related TEAEs. Six TEADRs in 4/77 patients (5.2%) led to permanent discontinuation of study medication, mostly injection site reactions.

No death occurred. One serious TEAE—a malignancy (pulmonary carcinoid tumor)—was considered not drug-related. One patient experienced a mild case of infectious mononucleosis which was rated as not drug-related since it started 71 days after the last dose of study medication. No other TEAEs of specific interest occurred. Four women were pregnant or breast-feeding during the study.

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ADEs were mild or moderate in severity except for one ADE rated as severe (PT 'injection site pain') which led to withdrawal of the device. No ADE resulted in reporting of a serious incident.

Device deficiencies such as stuck cartridge, liquid spill, and blocking of device occurred in 11/77 patients (14.3%). None led to reporting of an AE or SAE.

Conclusions:

- Satisfaction with self-injection was high in both, patients using ava, and patients using other devices in this study.
- Persistence of use also was high in both groups of patients. However, overall, it may have been influenced by patient demographics.
- The two device groups differed in key demographic variables:
  A majority of patients using ava were 18 to 44 years old, a similar number of patients using other devices was aged 18 to 44 years or 45 to 64 years.
  A clear majority of patients using ava was female, in the group of patients using other devices gender ratio was balanced.
  Rheumatoid arthritis as underlying disease was prominent in the ava group, psoriatic arthritis in the group of patients using other devices.
  More patients of the ava group had previously used self-injection devices for any indication, but more patients using other devices had previously used self-injector devices for the underlying disease. The majority of patients using other devices used biosimilars.
- Compliance was high (mean, median and 95% CI >80%) in both groups.
- TNF blockers were prescribed according to clinical guidelines/local standard of care in the majority of cases. Prescription was mostly not influenced by the type of device.
- Results of subgroup analyses show that satisfaction and persistence of use may be influenced by gender and age. Furthermore, device choice may be influenced by demographics.
- Safety profile was in-line with the known safety profile of CZP. No serious concerns arose. The benefit-risk ratio of CZP is not impacted by any of the safety-related findings in this PMCF study.

Report date: 19 May 2022