EUROPEAN COMMISSION

Expert decision and opinion in the context of the Clinical Evaluation Consultation Procedure (CECP)

Expert panels on medical devices and in vitro diagnostic devices (Expamed)

Contents

Scope of this expert opinion

This scientific opinion reflects the views of independent experts (MDR Article 106) on the clinical evaluation assessment report (CEAR) of the notified body. The advice is provided in the context of the clinical evaluation consultation procedure (CECP), which is an additional element of conformity assessment by notified bodies for specific high-risk devices (MDR Article 54 and Annex IX, Section 5.1).

The notified body is obliged to give due consideration to views expressed in the scientific opinion of the expert panel and in particular in case experts find the level of clinical evidence not sufficient or have serious concerns about the benefit-risk determination, the consistency of the clinical evidence with the intended purpose including the medical indication(s) or with the post-market clinical follow-up (PMCF) plan.

Having considered the expert views, the notified body must, if necessary, advise the manufacturer on possible actions, such as specific restrictions of the intended purpose, limitations on the duration of the certificate validity, specific post-market follow-up (PMCF) studies, adaption of instructions for use or the summary of safety and clinical performance (SSCP) or may impose other restrictions in its conformity assessment report.

In accordance with MDR Annex IX, 5.1.g., the notify body shall provide a full justification where it has not followed the advice of the expert panel in its conformity assessment report.

1 ADMINISTRATIVE INFORMATION

Date of reception of the dossier	25/08/2022
Notified Body number	0459
Medical device type	The application concerns the [redacted] anatomic shoulder prosthesis.
Intended purpose	The [redacted] anatomic shoulder prosthesis can be used for primary or revision of a shoulder arthroplasty, as hemiarthroplasty or as a total anatomic prosthesis.
Risk class / type	☒ class III implantable ☐ class IIb active device intended to administer or remove medicinal products(s)
Screening step: medical field / competence area	Orthopaedics, traumatology, rehabilitation, rheumatology / Joint replacements (hip, knee, shoulder)

PART 1 – DECISION OF SCREENING EXPERTS: NOTIFICATION OF NB AND COMMISSION REGARDING THE INTENTION TO PROVIDE AN OPINION

1.1 Decision of the screening experts

Table covers all three criteria, intended to support their consistent and conscientious application

Date of decision	15/09/2022
Screening panel decision	
Is there intention to provide a scientific opinion?	☒ **Yes** ☐ **No** ☐ **Insufficient information to reach a conclusion**
In case the information was found insufficient to reach a conclusion: summary of reasons	
Not applicable	
Summary as to why there is intention to provide an opinion	
There is concern about the high revision rate of this metal-backed glenoid component and metal-backed glenoid components in general.	
Summary as to why there is *no* intention to provide an opinion	
Not applicable	
Any other comments	
None	

1.2 Assessment of the three screening criteria

Criterion 1: Novelty of device under assessment and possible clinical / health impact
1.1 Novelty of device and/or of related clinical procedure
☒ No novelty: Neither device nor clinical procedure is novel ☐ Novelty: **Device** is novel ☐ Novelty: **Procedure** is novel
Short description of the novelty, including main dimension(s) of novelty
There is very little novelty – almost none – compared to the device which has been CE marked since 2007 (93/42 MDD). It shows no or negligible modification compared to a similar device already on the market (shoulder prosthesis) which is CE marked since 2007 (93/42 MDD). In 2022, indications were restricted, and two stem sizes were removed from market.
Overall degree of novelty

☐ Low level *or* ☐ Medium level *or* ☐ High level ☒ Not Applicable (neither the device nor the procedure is novel)
Uncertainties related to novelty
None
1.2 Possible negative clinical / health impact resulting from novelty
None
Estimated* severity of clinical and/or health impact.
☒ No clinical or health impact ☐ Minor clinical or health impact ☐ Moderate clinical or health impact ☐ Major clinical or health impact
Uncertainties related to clinical/health impact
None

Criterion 2: Scientifically valid health concerns leading to significantly adverse changes in the benefit-risk profile of a specific group / category of devices and relating to **a) Component(s)** **b) Source material(s)** **c) Impact on health in case of failure of the device**	
2.1 Information received from Secretariat:	☐ Yes ☒ No
2.2 Other information available to experts:	☒ Yes ☐ No
2.3 Reference to peer-reviewed publications/information sources:	
- AOANJRR (Australian Orthopaedic Association National Joint Replacement Registry) 2021 Annual Report pp. 304-305 - CEAR P-604427 pp. 46 (table), 63.	
In case information was used from either the Secretariat or other sources	
2.4 Groups/categories of devices:	
Metal-backed glenoid components in anatomical shoulder arthroplasty	
2.5 Relationship to component(s), source material(s) or health impact in case of device failure	
☒ Health concern(s) relates to **component(s)**	

☐ Health concern(s) relates to **source material(s)** ☐ Health concern(s) relates to **impact on health in case of device failure**
2.6 Description of health concern(s):
High revision rate
2.7 Reliability of information:
Reliable. Data from AOANJRR are based on very high number of cases
2.8 Relevance of information:
Highly relevant. The metal-backed glenoid under assessment is reported to have relatively high revision rate.
2.9 Summary:
The reported revision rate for metal-backed glenoid components is much higher than the revision rate for cemented components, and therefore we find a scientific opinion is necessary in order to approve or not approve this kind of device.

Criterion 3: Significant increase of serious incidents of a specific group / category of devices relevant for the device under assessment *(if information is available, it will always be provided by the expert panel secretariat)*	
3.1 Information received from secretariat?	☐ Yes ☒ No

1.3 Indication of appropriate thematic panel in case opinion is required

Indication of appropriate thematic panel and competence area		
	Expert panels	Medical and scientific/technical competence areas (these may correspond to sub-groups)
☒	**Orthopaedics, traumatology, rehabilitation, rheumatology**	☒ 1. Joint replacements (hip, knee, shoulder) ☐ 2. Spinal devices ☐ 3. Non-articulating devices, rehabilitation
☐	**Circulatory system**	☐ 1. Prosthetic heart valves and devices for heart valve repair ☐ 2. Cardiovascular stents (metallic and bio-resorbable) and vascular prostheses ☐ 3. Active implantable cardiac devices and electrophysiological devices ☐ 4. Structural interventions and new devices (e.g. LAA/PFO occluders, heart failure devices) ☐ 5. Cardiac surgery including extracorporeal membrane oxygenation, cardiopulmonary bypass devices, artificial hearts and left ventricular assist devices

☐	**Neurology**	☐ 1. Central and peripheral nervous system devices ☐ 2. Implants for hearing and vision (sensory recovery) ☐ 3. Neurosurgical devices
☐	**Respiratory, anaesthesiology, intensive care**	☐ Respiratory and anaesthetic devices
☐	**Endocrinology and diabetes**	☐ Endocrinology and diabetes devices
☐	**General and plastic surgery Dentistry**	☐ 1. Surgical implants and general surgery ☐ 2. Plastic surgery and wound care ☐ 3. Maxillofacial surgery & Devices for dentistry e.g. oral surgery, implantology, dental materials etc.
☐	**Obstetrics and gynaecology including reproductive medicine**	☐ Devices for obstetrics and gynaecology
☐	**Gastroenterology and hepatology**	☐ Devices for gastroenterology and hepatology
☐	**Nephrology and urology**	☐ Devices for nephrology and urology
☐	**Ophthalmology**	☐ Devices for ophthalmology

PART 2 – SCIENTIFIC OPINION OF THE THEMATIC EXPERT PANEL/SUB-GROUP

2.1 Information on panel and sub-group

Date of opinion	28/10/2022
Expert panel name	Orthopaedics, traumatology, rehabilitation, rheumatology
Sub-group of expert panel	Non-loadbearing joint replacements

2.2 Summary of expert panel opinion

- **Device description**

  The device is a shoulder implant which can be used as hemi-arthroplasty (HA: stem in humerus) or as anatomical total shoulder arthroplasty (ATSA: humerus and glenoid, ATSA) or a total reversed (RTSA) shoulder implant (humerus and glenoid). However, the reverse version is out of scope of this evaluation. The device consists of a metal humeral stem (cemented or uncemented), metal humeral head (centered and not centered) and a glenoid component. The latter has 2 versions:

  - a cementless metal backed one-peg design with 2 screws fixating the glenoid base plate, on the baseplate a polyethylene glenoid liner can be fixed (uncemented ATSA);

  - a cemented polyethylene glenoid component with 3 pegs fixed in the glenoid bone with cement (cemented ATSA).

  As for the reversed total shoulder version, the humeral head on the stem is changed for a "concave" polyethylene cup and the liner of at the glenoid metal backed base plate is changed for a convex metal "head" (i.e. reversed total shoulder implant, RTSA). The reversed total shoulder implant can only be used with the metal backed glenoid baseplate.

  Since the hemiarthroplasty and anatomical and reversed total shoulder implants are part of a modular shoulder system and have therefore interchangeable components, revision surgery relies on remaining components if components are exchanged during surgery (i.e. metal backed glenoid baseplate), and the whole shoulder system should be evaluated.

  The purpose of the shoulder system is to alleviate pain in a degenerative changed shoulder joint (majority of indications: osteoarthritis and arthritis) or in a fractured humeral head or full cuff tear and arthritis (reversed shoulder implant). A second goal is to improve function of the shoulder joint and thus improve quality of life for the patient.

  The mode of action of the shoulder device is to remove the degenerative joint surfaces of the humeral head or replace the fractured humeral head (hemiarthroplasty) with the metal head on a humeral stem articulating with the glenoid. In a reversed total shoulder implant design, the biomechanical principles of the reversed design (head and cup "reversed") are advantageous in presence of full tear of the rotator cuff. Depending on clinical indication (age, degeneration of glenoid and the rotator cuff) a total anatomical shoulder can be placed or a reversed total shoulder has to be implanted. The mode of action of the shoulder implants is an articulation of a metal

humeral head against glenoid bone (HA) or articulation of metal humeral head against the polyethylene glenoid (i.e. anatomical total shoulder -ATSA- in both cemented and uncemented glenoid version) or an articulation of a concave polyethylene humeral head with a convex metal glenoid head fixed on a metal backed glenoid baseplate (reversed total shoulder RTSA). Due to the different options of the modular shoulder implants, which are also interchangeable, it is better to address the implant as a modular shoulder system.

- **Novelty:** No novelty
- **Adequacy of clinical evidence assessment by notified body**

The clinical evidence presented by the manufacturer was not sufficiently critically appraised by the notified body (NB), and therefore the clinical evidence assessment by the NB is not adequate. Ranking of clinical evidence by the NB at level 4 (see MDCG 2020-6[1]) is correct. The CEAR did not provide any critical appraisal of data from registries other than the Australian and UK & Wales (NJR) registries, whereas other registries (e.g. New Zealand, Italy registry) are presented by the manufacturer in the CER and report on the same type of implants (although not on the actual implant under investigation).

Data from the Australian registry and other registries on similar implant types (but not the implant under investigation itself) are the following:

- revision rate for hemiarthroplasty (HA) at 10 years: Australia 11.8%; New Zealand 10.5%; NJR no data, Italian registry 8.4%;

- revision reverse shoulder arthroplasty (RTSA) at 10 years: Australia 6.3%, New Zealand 5.5%, Italy 7%;

- revision primary anatomic total shoulder (ATSA) at 10 years: Australia 11.6-13.2%; NJR no data, New Zealand 8.3%; Italy 5.5%. A similar device [redacted] as the anatomical total shoulder device under review showed 95.6% survival at 7 years (5.4% revision) in the NJR registry (UK and Wales) (n=1049).

Data from the internal study of the shoulder device (PMCF study 2021-6 [redacted] showed a revision rate at 5 years (60 months) of the HA group: 8.8%, ATSA cemented: 8.5% and ATSA uncemented: 13.3%. All groups had combined cemented and uncemented humeral stems.

Three articles were available on the device under evaluation [redacted] The NB should have made a more thorough critical appraisal next to the remarks made (small study, multiple surgeons, short follow-up). As an example, [redacted] report the results of a prospective study conducted on 143 total shoulder cases (cemented and cementless glenoid implant) with a mean follow-up of 3 years although only 37 cases (36 patients) have a follow-up of more than 2 years. Thus, a difference between accrual time and follow-up time is noted which points at methodological flaws, such as selection biases, and limits the interpretation of data.

In addition, there is likely a considerable overlap of patients since the author groups and hospitals where patient accrual was done have overlap. Thus, data are most likely not coming from independent sources. Even more, as the NB states, conflict of interest exists regarding the authors

[1] https://health.ec.europa.eu/system/files/2020-09/md_mdcg_2020_6_guidance_sufficient_clinical_evidence_en_0.pdf

of the study (e.g. authors are developer surgeons). It is worth noting that even these developer surgeons have significant complication rate.

In addition to these published articles, the manufacturer conducted a PMCF study (study n° 2021-6, [redacted] with a limited number of patients (706 patients) compared to the total number of shoulder prostheses implanted in clinical practice as mentioned by the manufacturer. This study presents retrospective data, with missing data for 7.6% of types of implants (i.e. HA, ATSA cemented and uncemented) and limited mean follow-up time (28-50 months). Data on revision and survival rates are performed up to 60 months of follow-up. As it is shown in the graphs of the survival analysis with follow-up beyond 1 year (e.g. ATSA cemented), the confidence intervals around the mean survival are wide, thus uncertainly on the estimate of the mean is important. The same applies for the 95% confidence intervals around the mean revision rate of HA, ATSA cemented and ATSA uncemented (see CER). The latter can most probably be explained by the very low patient numbers at these follow-up times. In its assessment (CEAR), the NB does not comment on this Various types of implants were studied: a mixture of different humeral stems (cemented and uncemented) for the HA (n=114), ATSA cemented (n=283) and ATSA uncemented (n=309), hampering the generalisability of data. The clinical (Constant) outcome scores were available in 17-40% of included patients for the 3 groups of implants (HA, ATSA cemented and uncemented), giving rise to selection and evaluation biases. Intraoperatively, 7 complications occurred, only in the ATSA uncemented group (which corresponds to 2.2% and not 0.3% as indicated in the CER and CEAR). Since no data on the claimed life-time of 10 years were given, the lifetime has been reconsidered and redefined by the NB at 5 years. But a lifetime of 5 years with the limited data available for the implant under review is too short to give an evidence based evaluation with respect to benefit and safety claims.

Finally, reporting of performance data of the shoulder implant system with 10-year follow-up was planned for September 2022, which dates prior to this report, but these data were not provided by the manufacturer. The NB acknowledges this but states: "Minor, major information is nevertheless available in the CER" although no data on 10-year results from the shoulder device under review are available in the CER

The conclusion of the NB is that the clinical evaluation was carried out satisfactory: clinical safety and performances of the shoulder implant have been correctly demonstrated. This whilst the data provided by the manufacturer (CER) show that the shoulder implant under review performs less well than other implants of the same type used for the same indications.

Finally, the expert panel insists on the fact that when a modular implantable shoulder system with interchangeable components is presented for review, the whole modular shoulder system should be evaluated, i.e., each version of the system (HA cemented/ uncemented, ATSA cemented/uncemented AND RTSA), contrary to what was done in this application.

- **Sufficiency of clinical evidence**

Data provided by the manufacturer (CER) are insufficient in view of the device's complexity (modular shoulder device) as discussed earlier in this report. In summary, important issues are: limited follow-up time, small sample size of patients in particular when considering the overall number of implanted shoulder prostheses. Regarding this aspect, three published articles with small sample sizes (n=51, n=30, n=143) were presented by the manufacturer in the CER. The

manufacturer did not completely apply their post-market surveillance protocol plan, as an example data with a 10-year follow-up are not presented contrary to what was initially planned. The internal data set (study n° 2021-6) is retrospective, 7.6% missing data on type of stem implant (cemented or uncemented). The PMCF clinical report (study n° 2021-6) had 13 patients at baseline with a list of missing data (see CER) and patient numbers higher than 706 are mentioned (i.e. 844, 852, 871) although the study is supposed to have included 706 patients in total. This raises the question whether more patients are missing. Another confusion on loss-to-follow-up comes from the CEAR report (page 42/72) which states that 400 patients were included, meaning 29% (of 706) of patients are missing. For that matter, attrition bias may be present but is not discussed. In addition, there is a discrepancy between the long accrual time (as of 2007) and data presented in this internal data report that only have a short follow-up. The PMCF plan aimed at a prospective study with a minimum of 500 shoulder implants (Europe / North America) in 20-30 centers collected in 3 years, with a prospective follow-up of the shoulder implant at 1, 3, and 6 months and 1, 2, 5, and 10 yrs.

Revision rates are as follows (assumption of the expert panel is that revisions were done at 60 months since the PMCF clinical study n° 2021-6 does not report this): HA 8.8% at 60 months (95% CI: 4.3-15.5%) ; ATSA cemented glenoid 8.5% (95% CI: 5.5-12.4%; ATSA uncemented glenoid 13.3% 95% CI: 9.7-17.6%).

Since no data on the claimed life-time of 10 years were collected, the lifetime has been reconsidered and redefined as 5 years by the NB. The latter is too short for benefit and safety claims for an implantable device for this indication and would need reassessment of valid and complete dataset including 10 year-data. The latter was actually part of the PMCF plan but was not executed. The manufacturer stated to have 10-year data in September 2022, but this was not made available to the expert panel. Thus, clinical performances and safety of this shoulder implant cannot be correctly demonstrated for the indicated patient groups. In addition, data at 5 years provided by the manufacturer show inferior results for the shoulder implant under review compared to the state-of-art within groups of similar shoulder implants (see earlier).

While one of the concerns was on the glenoid component fixation, no thorough analysis on glenoid fixation (radiographic analysis) or an implant migration study like RSA (stereophotogrammetric analysis) was done. One report mentions 30 CT scan evaluations, but data are not univocal interpretable (e.g. [redacted] studied radiolucencies about implant inadequately). Furthermore, radiolucencies are a surrogate end-point for progressive implant migration resulting in implant loosening, but these studies were not performed. Vigilance data (PSUR) are given for the ATSA cemented / uncemented shoulder implants, but it is not clear how these patients were selected, therefore under-reporting cannot be excluded.

The three published articles [redacted] have likely overlapping study populations since these studies were done by the same surgeons (authors of the publications) in the same hospitals. In addition to the short follow-up of these studies, authors were "shoulder" developer surgeons, that may also create a bias due to conflict of interest when interpreting the results (the latter was also acknowledged by the NB). A quick Cross search (citation check using the same author group) and the company's website led to the identification of 5 extra articles which were available at the time of the literature search done by the manufacturer. One study [redacted] showed a 17.3% revision rate at 5 years of follow-up for the primary shoulder implant under review (start n= 104 of which 18 were revised between 1 month and 61 months of follow-up). The mean

follow-up at which revision was performed was 15 months which indicates that most failures happened during early follow-up period. This revision rate of 17.3% is experienced in patients implanted by the developers of the prostheses. It is expected that the revision rate might be even higher when used by non-developers. However, no non-developer published clinical studies were found for this medical device to test this hypothesis.

As discussed above, the level of the evidence presented by the manufacturer can be considered as at level 4 (MDCG 2020- 6).

As a last remark, both the CER and CEAR show some inconstancies: both mention primary hip arthroplasty at two places in the report instead of shoulder arthroplasty and the terminology of "survival rate" is mixed-up with "revision rate".

- **Adequacy of benefit-risk determination**

As a general remark, the number of evaluated shoulder implants is small, in particular compared to the number of implanted shoulders reported by the manufacturer (2007-2020, Europe 19.354 stems, 13.591 uncemented glenoid components). The benefit-risk assessment done by the NB based on the data provided by the manufacturer (CER) was not adequate in the expert panel's opinion. This is in particular due to the limited available dataset with clinical outcome scores (i.e. Constant score). The CER report presents data on benefit and risk in a very limited selected groups of patients (study n 2021-6) which is likely not to be representative of the overall shoulder patient population for each of the shoulder implants' version (e.g. HA, ATSA cemented, etc.). In this regard, this retrospective study collected data (last follow-up date in 2021) of a cohort of patients who had one of the three types of shoulder implants (HA, ATSA cemented and uncemented glenoid) with unknown selection process (e.g. loss-to-follow-up at 60 months). The way this group of patients was selected cannot be known from the report. According to the CER, 13 patients died, had unknown or missing data. Confusion on numbers of evaluated patients exists due to patient numbers in the CER which do not match the 706 patients evaluated (see previous remark on loss-to-follow-up). Second confusion is that the CEAR mentions 400 patients being evaluating (thus 29% loss-to-follow-up). Of this group only 23-40% had clinical outcome scores (i.e. Constant score). The analysis of this limited patient group with clinical Constant scores (77-60% of loss-to-follow-up) of the baseline group has limited clinical value. A positive aspect is that these clinical outcome scores included an analysis on the MCID (minimal clinical important difference). A fundamental question regarding this cohort of patients is how they were selected and the potential selection bias.

With respect to risk, the CER gives results on perioperative and postoperative complications observed in the internal study (i.e. 2021-6 [redacted]. This study included n= 283 cemented glenoid ATSA, n= 309 uncemented glenoid ATSA. The ATSA uncemented glenoid had 7.7% complications (glenoid fracture, disassembly, glenoid loosening, metallosis, wear); the ATSA cemented glenoid component had 13.5% complications (the majority being loosening of the implant: 7.7%). No follow-up time is given for the postoperative time-period during which the complications were recorded. As for vigilance data (CER), there is a lack of information on the selection criteria regarding shoulder prostheses and patients, questions on how the groups were defined, how patients were selected, included, evaluated (nominator and denominator numbers are missing); if the percentages of complications were calculated taking into account the number of patients at the start of the 2021-6 internal study, how many patients were loss-to-follow-up etc. All this information would have been necessary to interpret the results and compare them with

those of groups of similar implants. Since implants (stem and glenoid components) rely on bone fixation, which determines their durability at long-term (i.e. > 10 years), an adequate radiographic analysis would have been expected, either in a large group with CT or radiographic analysis or in a small group with a highly accurate measurement of implant migration (i.e. RSA, stereophotogrammetric analysis). In this case radiographic analyses were done only in small groups, with a non-adequate technique (as mentioned also by NB in CEAR).

The manufacturer reports data on complications for ATSA (without stratification according to cemented and uncemented glenoid implant) from NJR 2022 report (registry of UK & Wales & North Ireland) that show 9.0% of complications.

The manufacturer compares revision rates at 5 years of the shoulder implant under review with a similar shoulder implant [redacted] The latter had higher revision rates for HA (28% versus 13.5% for the shoulder prosthesis under review), for ATSA cemented (10.8% versus 6.6% for shoulder prosthesis under review) and comparable revision rates for ATSA uncemented (14.3% versus 15.4% for the shoulder prosthesis under review). Two important methodological issues have to be mentioned, first, the confidence intervals of these 5-year revision rates are not reported which makes it not possible to conclude on the potential differences between the two implants, secondly the shoulder implant under review should have been compared with state-of-the-art shoulder implants from real-world data available in registries (and provided in the CER of the manufacturer but not discussed by the notified body).

- **Consistency of clinical evidence with purpose / medical indication(s)**

  The way clinical data was collected is consistent with the purpose and medical indication for shoulder implants, but the supported data for the shoulder implant under review as well as the methodology used to analyse this data are not consistent. There is a lack of information to generate good clinical evidence, thus a MDCG 2020-6 level 4 is given in terms of level of evidence. The protocol of the PMCF study 2021-06 was not properly applied instead the manufacturer presented an internal retrospective dataset (PMCF study no 2021-6, [redacted] with a limited number of patients with short follow-up (see previous sections). This internal retrospective dataset has considerable loss-to-follow-up data. Clinical outcome (Constant) scores are also prone to selection bias due to high loss-of-follow-up rates (see earlier). Revision data are presented for a selected retrospective Internal cohort. Complication and vigilance data come from a selected group of patients (see earlier). The manufacturer provides data on the revision rate for groups of similar shoulder implants from multiple registries (e.g. Australia, Italy, UK& Wales, etc.). Supported data from 3 published articles (see earlier) are on small patient groups, with short follow-up and present methodological flaws (multiple confounding factors such as many surgeons, different shoulder devices, different diagnoses, developer surgeons, possible overlap of patients in the three articles etc. with no reported mitigation methods that considerably limit the internal validity of these studies).

- **Consistency of clinical evidence with PMCF plan:**

  Although a post-market clinical study has been conducted (PMCF study 2021-6) analysing complications, survival of the different shoulder implant types, revision of these types, clinical (Constant) outcome scores, etc., data quality is hampered due to the lack of information on how the 706 patients were selected, how many patients were loss-to-follow-up at successive follow-up

times during the 60 months. The latter is reflected in wide 95% confidence intervals around the mean survival and mean revision rates of the different types of shoulder implants. Therefore, no consistency exists between the clinical evidence and the PMCF plan. The clinical study report (see CER study 2021-06 _protocol v1.0_20210507) states that the primary objective is to "describe the performance and safety of the reviewed prosthesis in long-term shoulder arthroplasty" but clinical evidence at 10 years was not presented. It also states that secondary objectives include "description of patient and implant characteristics". This is fundamentally wrong since patient and implant descriptions cannot be an objective but are a fundamental part of the study inclusion criteria. Furthermore, the presented evaluation has some significant methodological flaws (see earlier in this report, e.g. lost follow-up, heterogenous patient groups etc). The main outcome is about long-term performance and safety (CER), the latter is not shown. A minimum of 400 patients was planned to be included, the expected number was 1200 patients (CER). The actual number was 706 shoulder implants of which 13 patient data were missing, unknown or patients died (CER). The latter makes the internal validity of the study extremely limited. As stated previously this retrospective study may have considerable selection bias. No formal analysis of selected and (non)included patients was done (i.e. sensitivity analysis: type of patients, implants etc) in order to control selection bias.

As for the new PMCF plan for a clinical study (no 2020-03 version2 date 8/7/21), the authors have again a wrong definition of secondary endpoints that include "patient and implant characteristics, diagnoses, preoperative state joint". This is fundamentally wrong since patient and implant descriptions cannot be an endpoint but are a fundamental part of the inclusion criteria. Expected inclusion is of 500 patients in Europe and USA. In the protocol of this study, implant fixation analysis has been added but no formal description of radiographic implant evaluation is described. This is however mentioned in the follow-up schedule table. Furthermore, considering the output of the PMCF clinical study (2021-6) which did not reflect the protocol, it is advised for this study to coordinate logistics and feedback on study number accrual and data quality during the study inclusion and evaluation.

- **Overall conclusions and recommendations on clinical evaluation**

The clinical evidence available on the device is considered by the panel to be insufficient for the intended purposes. Clinical evidence is based on data from a very limited number of patients with short follow-up. Available data on the device comes in total from 3 publications and one internal study. Two of the 3 publications seem to have overlapping and small populations with short follow-up. These studies show many sources of variability without any measures to mitigate them that considerably limits their internal validity. No thorough analysis on the glenoid implant fixation or implant movement during the short follow-up time has been performed. In one report, 30 CT scan evaluations were done, but implant fixation has not been studied by migration studies. Considering the limited available follow-up on the device, the latter would be required to get more reliable proof of long-term implant stability e.g., after 10 years.

2.3 Detailed aspects of the opinion as required by MDR Annex IX Section 5.1

Opinion of the expert panel on the specific aspects of the clinical evaluation assessment report of the notified body (CEAR)[2]
1. Overall opinion on the NB's assessment of the adequacy of the manufacturer's clinical evaluation report
The CEAR gives to some extent a critical appraisal of the three articles [redacted] and the internal retrospective report (PMCF study no 2021-6) presented by the manufacturer, but the NB did not provide a thorough and sufficient detailed assessment of the clinical data for the reasons discussed extensively in the previous sections. Although the NB did review the 3 articles on the implant and identified some of the methodological flaws, the critical appraisal of these articles could have been more rigorous and should have been jointly analysed with the internal clinical data of the manufacturer (PMCF study 2021-6, [redacted] as well as data from registries on similar groups of devices so as to have an integrated evaluation of all available data on the device under review. In summary, the data provided by the manufacturer (e.g. articles, internal 2021-6, registry data) should be interpreted in conjunction with each other, thus compiling evidence for an overall evaluation of the shoulder system under review. The latter will result in a more evidence-based appraisal of the clinical evidence given by the manufacturer in the CER to support their shoulder system.
2. Opinion on the NB's assessment of the sufficiency of the clinical evidence provided by the manufacturer
Clinical evidence is not robust enough and not sufficient. As described in the previous sections, data on the device is based on 4 clinical study reports including 3 articles that seem to have overlapping populations with short follow-up, and many sources of variability and uncertainty (small patient groups with many surgeons, unknown selection criteria, loss-to-follow-up -20% evaluated at 2 year-, different indications.) that is neither controlled nor discussed, threatening the study's internal validity. In addition, no thorough analysis was performed on glenoid fixation or implant movement (i.e. radiographic analysis was not adequate for glenoid fixation and too little patients) during the short follow-up of the three studies [redacted] Implant fixation has not been studied by analysing systematic implant-bone interface nor implant migration studies were done. Since the follow-up is short, the latter is required to give more reliable proof of long-term implant stability e.g., after 10 years. The implant (humeral stem and glenoid) should be reliably fixed to the bone (i.e. no implant migration). The NB reported some of the limitations of the 3 articles but did not perform a critical appraisal of all the data provided in the CER (i.e. did not discuss the data of registries into full extent). Furthermore, the NB accepted that no 10-year data were provided for this evaluation (but only in September 2022). In addition, important studies were missing from the literature search of the manufacturer and this was not identified by the NB. In particular, a study [redacted] reports a revision rate of 17.3% at 5 years when the device was used by the developers. Even if the reversed total shoulder (RTSA) system is out of scope of this evaluation, the question remains concerning its clinical

[2] According to Annex IX Section 5.1 of Regulation (EU) 2017/745 - Assessment procedure for certain class III and class IIb devices.

evaluation if this implant is still on the market since the RTSA is part of this overall modular shoulder system. As argued earlier by the expert panel, all possible options and configurations should be evaluated considering the different implant options, primary as well as revision after changing components. Thus, a separate analysis of each possible "shoulder implant" of the shoulder-system should have been done in order to make an adequate benefit-risk assessment of each of the possible "shoulder implant".

3. Opinion on the NB's assessment of the adequacy of the manufacturer's benefit-risk determination

The benefit-risk ratio of the device could have been more critically appraised by the NB. The benefit analysis is based on clinical outcome data (Constant shoulder score) from a limited selected group of patients implanted with the shoulder prosthesis without a control group. The claimed clinical benefit should be weighed against the reported higher revision rate of the shoulder implant under review. In addition, the manufacturer claims that the revision rate of this modular shoulder system is high because it is easy to revise. But the manufacturer does not provide data before and after revision, so the benefit for the patient after such a potentially easy revision cannot be assessed. The manufacturer presents data on benefit and risk in a very limited selected group of patients which is likely not to be representative of the overall shoulder patient population for each of the shoulder implants (e.g. HA, ATSA cemented, etc.). As regards the 3 shoulder implant groups (HA, ATSA cemented and uncemented glenoid) only 23-40% of patient outcome scores were available (see previous section). The analysis of this small patient group (77-60% lost-to-follow-up) with clinical scores (Constant shoulder score) has very limited value.

The NB only reported some of the previously listed limitations but did not perform a critical appraisal of all the available data on the shoulder system under review as well as on similar devices (CER, e.g. all registry data). In addition, the NB accepted that 10-year follow-up data were not provided until September 2022.

4. Opinion on the NB's assessment of the consistency of the manufacturer's clinical evidence with the intended purpose, including medical indication(s)

According to the notified body's assessment, the information supplied by the manufacturer adequately provides the safety and performance information relevant to the user. In addition, the views of the notified body are that Indication and contra-indication, expected performance, limitations, warning and precaution, potential side-effects are consistent and written in a clear and understandable way.

However, in the expert panel's opinion, the clinical evidence in the CER with respect to the shoulder implant under review is not sufficient compared to the state-of-the-art generic group of shoulder implants given indications, contra-indications and potential side effects

No critical appraisal was done on the survival and revision data (survival graphs at follow-up at 1 year and longer (e.g. ATSA cemented) have wide confidence intervals around the mean, thus uncertainly on the estimate of the mean is important. The same applies for the 95% confidence intervals around the mean revision rate of HA, ATSA cemented and ATSA uncemented. The latter is most probably a reflection of the very low patient numbers at these follow-up moments.

Incoherence exists between the number of evaluated patients in the CER and CEAR: CEAR states 400 patients, thus 29% loss to follow-up while CER states 13 patients (missing, unknown, dead). In addition,

according to patient numbers in the "death and causes" table, patient numbering is higher than the total number of 706 included patients, suggesting that more patient are probably lost to follow-up. The latter puts forward the question about the selection process of this clinical study (study 2021-6).

Contrary to the NB assessment, the opinion of the expert panel is that the clinical evidence provided by the manufacturer is not sufficient to demonstrate the expected performance, safety, limitations, warnings and precautions of the device due to:

- the aforementioned reasons, in particular the limited number of patients, with unknown selection criteria and short follow-up
- - the absence of adequate radiographic analyis on implant fixation (glenoid) was done neither in the three publicatioms nor the internal clinical study.

5. Opinion on the NB's assessment of the consistency of the manufacturer's clinical evidence with the PMCF plan

The annual PMCF update activities includes:

- screening of peer-reviewed scientific literature by searching various databases and health organisations' websites with appraisal according to standard methodology
- evaluation of clinical data from high validity arthroplasty registries
- collection and review of post-market clinical investigation data from post-market studies on shoulder prostheses marketed by the manufacturer:
    - PMCF study #2021-06 [redacted], retrospective, observational, non-comparative study, end date in June 2021
    - PMCF study # 2020-03, retrospective and prospective, observational, non-comparative study conducted at international level (EU and USA) to be launched 2nd semester 2022. This study will include a minimum of 500 patients implanted with any type of shoulder prostheses marketed by the manufacturer.
- customer/user feedback surveys will be collected with accordance to Procedure for Post Market Surveillance and Procedure for Cumulative Post Market Surveillance Activities
- continued suitability of the PMCF Plan will be assessed as each clinical evaluation is conducted and the PMCF plan will be modified if necessary

The current PMCF plan is not adequate enough to address the identified gaps of clinical evidence for this shoulder implant in relation with the issues raised previously (see in particular section 2.2 on Consistency of clinical evidence with PMCF plan). Some these issues have been identified by the NB but the NB did not perform a critical appraisal of the two PMCF studies (2021-6, 2020-3), in particular regarding primary and secondary end-points as well as measures to ensure data quality and validity.

2.4 Overall conclusions and recommendations

Data of the shoulder implant system under review does not meet minimum standards when compared to state-of-the-art implants of the similar group of shoulder implants in particular revision rates and complications. The latter is substantiated by the high revision rate of the evaluated anatomical total shoulder both with cemented as well as uncemented glenoid components compared to data of similar

groups of shoulder implants in national registries (Italy, NJR, Australia, New Zealand). A well-designed PMCF clinical protocol was not executed as planned. Instead, an internal retrospective dataset of shoulder implant patients was presented, with limited follow-up (with respect to the possible accrual time since 2007), limited patient number (with respect to the overall implants used in Europe and globally) and considerable numbers of loss-to-follow-up. The planned 10-year clinical dataset for September 2022 is not provided in the CER. Finally, the literature search was not adequate as it only retrieved 3 articles, while at least 5 additional articles were found at the time of the literature search performed by the manufacturer. These articles were potentially relevant and would have increased the number of available publications to 8 instead of 3, significantly increasing the quantity of available data on the device.

Recommendations:

- If a complex modular shoulder arthroplasty system with interchangeable components is under review, all possible shoulder implants and combinations (HA, ATSA, including in this current case the RTSA with its different cemented and uncemented versions) should be evaluated.
- All information provided by the manufacturer should be taken into account and jointly analysed considering the different sources of information and the reasons for missing data (loss-to-follow-up). Included data should minimize the risk of selection bias or at least, this should be discussed and taken into consideration in the final analysis.
- NB should ensure that all published articles have been identified and presented by the manufacturer (in this case, at least 5 articles were missing, see previous paragraphs)
- Data from registries with high validity should be considered. However, this data should not be limited to the revision rates of similar implants but should also include the revision rates of the implant under evaluation.
- Since a joint replacing implant relies on bone fixation (i.e. loose implants cause pain and disability), radiographic evaluation of the implant-bone interface or data on implant migration within the bone should be carried out during a limited time period. Implant migration and ultimate implant loosening can be measured with RSA (radiostereometry) or comparable techniques so as to get as many objective quantitative data as possible in addition to clinical outcome scores in view of patient safety.

- A thorough and robust literature search is at the core of a reliable systematic review. Such literature search and study selection should be conducted by qualified experts according to internationally accepted guidelines (e.g. PRISMA or MOOSE) in order to maximize the validity of the report.

2.5 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable[3]
Has the Secretariat provided information from stakeholders?
☐ Yes ☒ No
Summary of the information that was taken into account and how it was taken into account.
Not applicable

2.6 Divergent positions in case no consensus was reached

Summary of divergent positions
Not applicable

Please indicate how many of the experts of the panel or sub-group had divergent views
Not applicable

[3] According to Article 106.4 of Regulation (EU) 2017/745, expert panels shall take into account relevant information provided by stakeholders including patients' organisations and healthcare professionals when preparing their scientific opinions.