Supplementary data related to the manuscript entitled:

Flare-up after Maxillofacial Surgery in a Patient with Fibrodysplasia Ossificans Progressiva: an \[^{18}\text{F}]\text{-NaF PET/CT Study and a Systematic Review}

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Supplementary data included are:

Legends to supplementary Figure 1

Supplementary Tables 1, 2 and 3.
Legends Supplementary Figure 1

Supplementary Figure 1

Flow diagram of the included studies in the systematic review on FOP and maxillofacial surgery
Supplementary Figure 1

Records identified through database searching (n = 169)

Records after duplicates removed (n = 168)

Records screened based on title (n = 168)

Records screened based on abstract (n = 83)

Full-text articles assessed for eligibility (n = 18)

Studies included in the review (n = 9)

Records excluded, with reasons (n = 85)
- No FOP (76)
- No clinical/surgery (9)

Records excluded, with reasons (n = 65)
- No FOP (33)
- No clinical/surgery (32)

Full-text articles excluded, with reasons (n = 9)
- No FOP (4)
- No surgery/ follow-up (3)
- No original papers/review (1)
- Article was not in English language (1)
Supplementary Table 1

Key Words, (MESH) terms and Strategy used and combined for the systematic review on maxillofacial surgery in FOP

| Review Key Words | Mesh terms |
|------------------|------------|
| FOP              | "Myositis Ossificans"[Mesh] OR fibrodysplasia ossificans progressiva*[tiab] OR myositis ossificans*[tiab] OR stone man*[tiab] OR acvr1*[tiab] |
| Surgery          | "surgery" [Subheading] OR "Surgical Procedures, Operative"[Mesh] OR "Surgeons"[Mesh] OR "Perioperative Period"[Mesh] OR "Perioperative Care"[Mesh] OR "Anesthesia"[Mesh] OR "Osteotomy"[Mesh] OR "Orthognathic Surgical Procedures"[Mesh] OR surger*[tiab] OR surgical*[tiab] OR surgeon*[tiab] OR operation*[tiab] OR operative*[tiab] OR perioperati*[tiab] OR anesthe*[tiab] OR anaesthe*[tiab] OR incisi*[tiab] OR extracti*[tiab] OR excisi*[tiab] OR ostectom*[tiab] OR osteotom*[tiab] OR coronoid*[tiab] OR invasive*[tiab] OR restorati*[tiab] |
| Jaw              | "Facial Bones"[Mesh] OR "Tooth"[Mesh] OR "Microstomia"[Mesh] OR "Mouth"[Mesh] OR "Dental Caries"[Mesh] OR "Masticatory Muscles"[Mesh] OR "Mastication"[Mesh] OR restricted mouth*[tiab] OR microstom*[tiab] OR oral*[tiab] OR orally*[tiab] OR masticat*[tiab] OR dental*[tiab] OR periodontal*[tiab] OR molar*[tiab] OR jaw*[tiab] OR jaws*[tiab] OR mandib*[tiab] OR maxill*[tiab] OR zygoma*[tiab] OR tooth*[tiab] OR teeth*[tiab] OR mouth*[tiab] OR locking*[tiab] OR locked*[tiab] OR interocclus*[tiab] OR occlus*[tiab] OR malocclus*[tiab] OR caries*[tiab] OR teeth*[tiab] OR tooth*[tiab] OR fusion*[tiab] OR fixati*[tiab] OR ankylos*[tiab] OR jawlock*[tiab] |

| Review process | Procedure |
|----------------|-----------|
| Strategy       | The review process included the following strategy: excluded were articles not investigating FOP or jaw surgery. All identified titles (n=169) were independently evaluated by two reviewers (ME, CN). We selected only those studies that were related to both FOP and jaw surgery. After scrutinizing the remaining 18 articles, 9 articles were excluded because they were not related to FOP and jaw surgery, either not originally or not in the English language. |

FOP= Fibrodysplasia ossificans progressiva; ME=Marelise Eekhoff; CN=Coen Netelenbos
Supplementary Table 2

Laboratory results pre- and post-maxillofacial surgery

| Blood tests                  | Pre surgery | Post surgery flare-up | No clinical flare-up |
|------------------------------|-------------|-----------------------|----------------------|
|                              | 1 year   | 1 week | 1 month | 1.5 months | 2.5 months | 1 year   |
| CRP (N<8 mg/L)               | <2.5     | <2.5   | <2.5    | 8          | 4          |          |
| ESR (N<20 mm/hr)             | 8        |        |         |            |            |          |
| Hb (N 7.5-10 mmol/L)         | 8.1      | 7.9    | 7.9     | 7.5        | 8.9        |          |
| Leucocytes (N 4-10 x10⁹/L)   | 9.5      | 22.5   | 14      |            |            |          |
| MDRD (N>60 mL/min/1.73 m²)   | >90      | >90    | >90     |            |            |          |
| Calcium (N 2.2-2.6 mmol/L)   | 2.32     |        | 2.35    |            |            | 2.32     |
| Phosphate (N 0.7-1.4 mmol/L) | 1.0      |        |         |            |            |          |
| Albumin (N 35-52 G/L)        |          | 36     |         |            |            | 37       |
| ALP (N 0-120 U/L)            | 57       | 60     | 14      | 6          | 56         |          |
| GGT (N 0-40 U/L)             | 10       |        |         |            |            |          |
| CK (N 0-145 U/L)             |          |        | 49      |            |            | 51       |
| Vit D (N 25-150 nmol/L)      | 104      |        | 1.5     | 1.6        | 39         |          |
| Osteocalcin (0.5-2.2 mmol/L) |          |        |         |            |            |          |
| P1NP (N 19-83 µG/I)          | 29       |        | 22      | 37         | 39         |          |
| 1CTP (N 2.1-5.6 µG/I)        | 4.6      |        |         |            |            |          |
| CTX (N <573 ng/L)            |          |        | 55      |            |            |          |

| Urinary tests                |            | | | | | |
| Hydroxyproline (mmol/L)      | 0.429      |        |         |            |            | 0.103    |
| Creatinine (mmol/L)          | 34.98      |        |         |            |            | 6.13     |

CRP=C-Reactive Protein, ESR=Erythrocyte Sedimentation Rate, Hb=hemoglobin,

MDRD= Modification of Diet in Renal Disease Study equation,

ALP= total alkaline phosphatase, CK=Creatine Kinase, Vit D= vitamin 25(OH)D,

P1NP= type 1 procollagen N-terminal, 1CTP=cross-linked carboxyterminal telopeptide of type I collagen, CTX=C-terminal telopeptide (CTX).
**Supplementary Table 3**

Summary of the included articles on maxillofacial surgery in FOP identified by the systematic review

| Authors          | Gender (age in years) severity FOP | FOP diagnosis (age) | Reason for jaw surgery | Surgical removal and therapy | Follow-up time and therapy | Final situation (decrease of ID opening) | Improved jaw opening/increased quality of life |
|------------------|------------------------------------|--------------------|------------------------|------------------------------|-----------------------------|----------------------------------------|---------------------------------------------|
| Connor et al. 1982<sup>(1)</sup> | Female (15-34) | ? | Limitation jaw movement | HO | 4 months | Total occlusion | No improvement |
| Seguin et al. 1987<sup>(2)</sup> | ? (16) | After surgery | Limitation jaw movement | HO | ? | Recurrence HO | No improvement |
| Crofford et al. 1990<sup>(3)</sup> | Male A (21) extensive HO Male B (16) dextroscoliosis | A (13) B (15,5) | A: Jaw immobilization B: ID 5 mm HO mandibular to pterygoid | A: Bridge of zygomatic arch to coronoid B: HO medial pterygoid muscle | A: 8 months etidronate B: 2 months isotretinoin and etidronate | A: ID 2 mm 1 month after operation B: ID 4 mm 2 months after operation | Apparently in both patients deterioration (no improvement) |
| Aslan et al. 1999<sup>(4)</sup> | Female (?) with joint restrictions | ? | Bilateral trismus | HO masseter muscle | 1 year etidronate | Total lockjaw | No improvement |
| Chichareon et al 1999<sup>(5)</sup> | Male (3) torticollis | After third jaw operation (5?) | a) ID 2cm due to submandibular osteochondroma b) ID 1mm by new HO bridging c) ID 5 mm by recurrent HO | a) Osteochondroma (2 cm) at lower border mandibula b) HO and coronoidectomy c) HO after b) (anesthesia: tracheostomy) | a) 10 months physiotherapy forced opening b) 5 months with physiotherapy c) one month | a) ID 1 mm b) ID 5mm c) ID decrease rapidly within 1 month | Three operations (a, b, c) leading to deterioration with new HO cheek and neck (no improvement) |
| Study Reference        | Age | Sex | Symptoms | Treatments                                                                 | Outcome                                                                 | Literature References |
|------------------------|-----|-----|----------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------|-----------------------|
| Herford et al 2003(6)  | 24  | Male | Complete trismus for 10 years | 1 cm HO between zygoma sup. and coronoid process | 1 year rigorous physiotherapy | ID 15 mm | Improvement/increased quality of life |
| Wadenya et al. 2010(7) | 10  | Male | Before second operation (20) | a) After trauma at age 9 progressive limited opening  
  b) Complete trismus after first operation  
  c) Buccal approach for dental care only | a) 1st operation HO condylar head-temporal bone  
  b) 2nd operation bilat. subcondylar osteotomies,  
  c) 3rd procedure fiberoptic bronchoscopy | a) time follow-up lost  
  b) after 10 years lost in follow-up  
  c) no follow-up | Two operations (a, b) leading to deterioration (no improvement) |
| Carvalho et al. 2011(8) | 8   | Male | Submandibular and post-neck swellings | 14 years | Jaw restriction retrognatism | Apparently deterioration (no improvement) |
| Kriegbaum et al. 2013(9) | 26  | Male | Only jaw involvement after third operation (29) | ID 12 mm | a) 1st operation bony fusion mandible and zygomatic arch  
  b) 2nd operation bony fusion  
  c) 3rd operation preauricular incision, extensive resection of the HO | a) 1 year dilation and physiotherapy  
  b) salazopyrine 1 year  
  c) 6 years, later etidronate and vigorous exercise | a) ID 12 mm after one year  
  b) ID decrease thereafter  
  c) ID 8 mm due to massive HO recurrence | Eventually no improvement |
Reference List of supplementary Table 3

(1) Connor JM, Evans DA. Extra-articular ankylosis in fibrodysplasia ossificans progressiva. Br J Oral Surg 1982 Jun;20(2):117-21.

(2) Seguin P, Delmas P, Bouvier R, Freidel M. [Permanent constriction of the jaws due to progressive ossifying myositis]. Rev Stomatol Chir Maxillofac 1987;88(3):190-5.

(3) Crofford LJ, Brahim JS, Zasloff MA, Marini JC. Failure of surgery and isotretinoin to relieve jaw immobilization in fibrodysplasia ossificans progressiva: report of two cases. J Oral Maxillofac Surg 1990 Feb;48(2):204-8.

(4) Aslan G, Celik F, Gorgu M. Unusual ankylosis of the jaw due to fibrodysplasia ossificans progressiva. Ann Plast Surg 1999 Nov;43(5):576-8.

(5) Chichareon V, Arpornmaeklong P, Donsakul N. Fibrodysplasia ossificans progressiva and associated osteochondroma of the coronoid process in a child. Plast Reconstr Surg 1999 Apr;103(4):1238-43.

(6) Herford AS, Boyne PJ. Ankylosis of the jaw in a patient with fibrodysplasia ossificans progressiva. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003 Dec;96(6):680-4.

(7) Wadenya R, Fulcher M, Grunwald T, Nussbaum B, Grunwald Z. A description of two surgical and anesthetic management techniques used for a patient with fibrodysplasia ossificans progressiva. Spec Care Dentist 2010 May;30(3):106-9.

(8) Carvalho DR, Farage L, Martins BJ, Speck-Martins CE. Craniofacial findings in fibrodysplasia ossificans progressiva: computerized tomography evaluation. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011 Apr;111(4):499-502.

(9) Kriegbaum RK, Hillerup S. Fibrodysplasia ossificans progressiva (FOP): report of a case with extra-articular ankylosis of the mandible. J Craniomaxillofac Surg 2013 Dec;41(8):856-60.