

Biodegradierbares Knochenersatzmaterial als Wirkstoffträger

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Heraeus Medical GmbH





Heraeus Medical: Short-profile

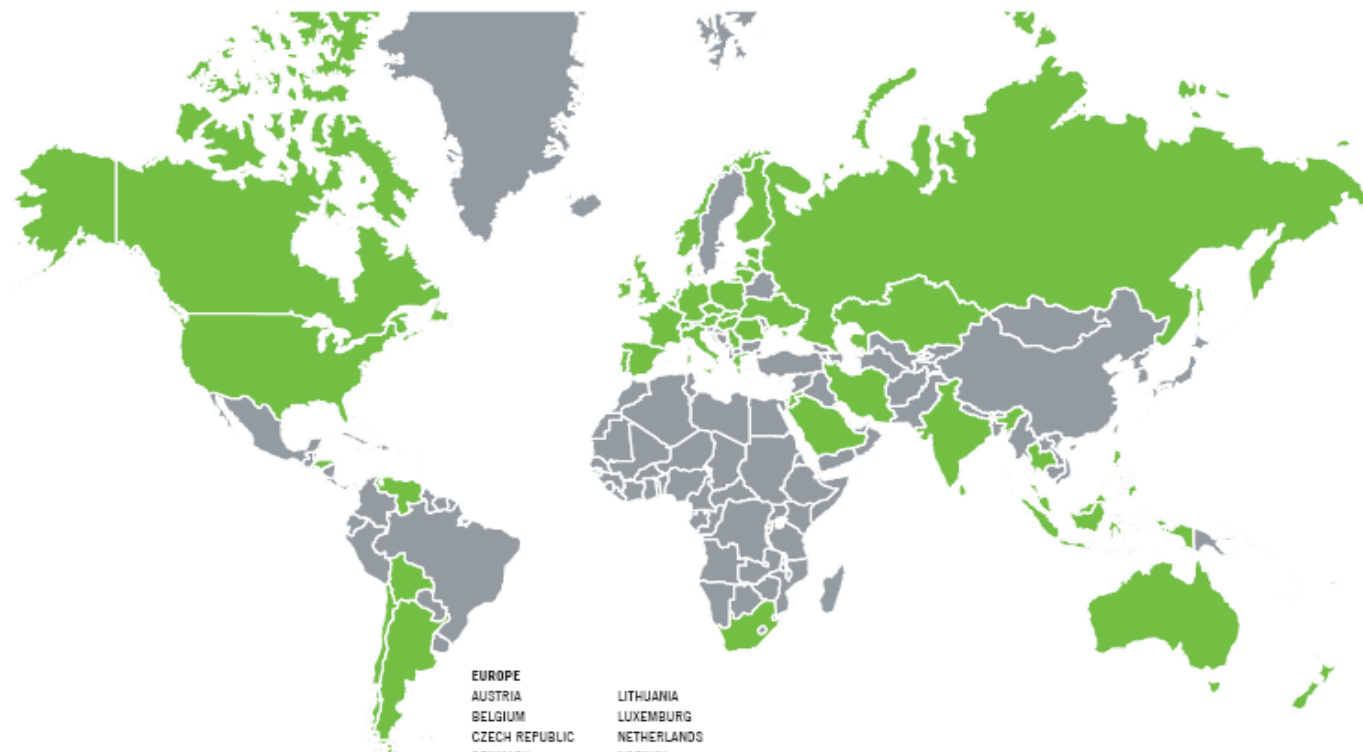
- ▶ Heraeus is a global precious metals and technology Group, with HQ in Germany; family-owned; with revenues of €16 billion in 2008; 3,000 employees in over 110 subsidiaries
- ▶ Heraeus Medical is a biomaterials and biosurgery company that develops, manufactures and markets innovative products and technologies to make an essential contribution to improving surgical results in bone and joint surgery in over 50 countries.

HQ in Wehrheim (close to Frankfurt)/Germany)

- ▶ biomaterials platform: products for the fixation of orthopedic joint replacements and the stabilization of spinal fractures
- ▶ biosurgery platform: anti-bacterial coatings for any Medical device
- ▶ Heraeus Medical has an extensive educational platform, both live and online.
- ▶ Member of BV Med, Eucomed, AdvaMed, ABHI, Snitem, Swedish Medtech, Assobiomedica,



Geographical presence



- | | | | | | |
|----------------|----------------|----------------|--------------------|-------------|----------------|
| AMERICA | EUROPE | | MIDDLE EAST | ASIA | |
| BOLIVIA | AUSTRIA | LITHUANIA | IRAN | INDIA | |
| CANADA | BELGIUM | LUXEMBURG | ISRAEL | INDONESIA | |
| CHILE | CZECH REPUBLIC | NETHERLANDS | JORDAN | KAZAKHSTAN | |
| HONDURAS | DENMARK | NORWAY | KUWAIT | MALAYSIA | |
| USA | ESTONIA | POLAND | SAUDI ARABIA | PHILIPPINES | |
| | FINLAND | PORTUGAL | | SINGAPORE | |
| | FRANCE | ROMANIA | | SRI LANKA | OZEANIA |
| | GERMANY | RUSSIA | | THAILAND | AUSTRALIA |
| | GREECE | SERBIA | | | NEW ZEALAND |
| | HUNGARY | SLOVAKIA | | | |
| | IRELAND | SPAIN | | | |
| | ITALY | SWITZERLAND | | | |
| | KOSOVO | UNITED KINGDOM | AFRICA | | |
| | LATVIA | UKRAINE | SOUTH AFRICA | | |



Heraeus Medical - Focus

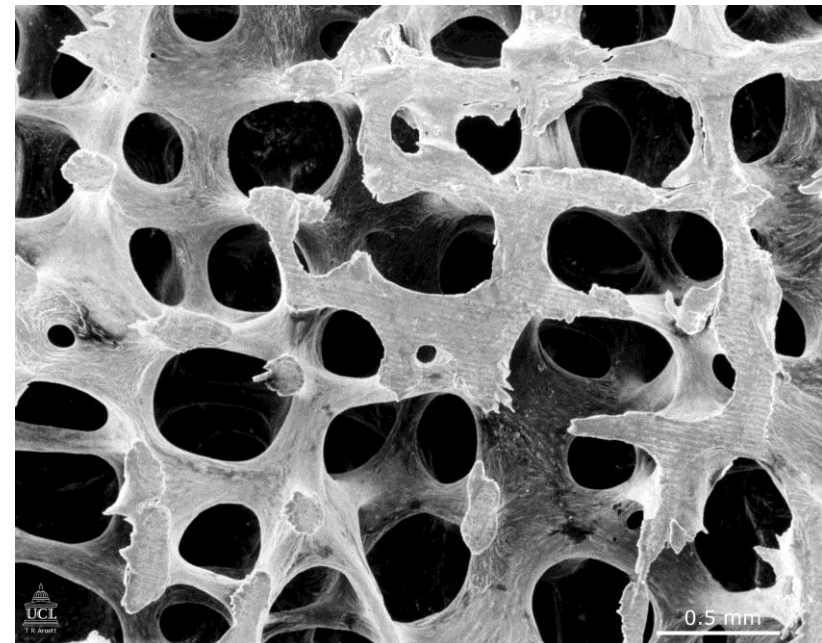


	customers
Reconstruction & Trauma	Trauma surgeons, orthopaedic surgeons, pharmacists
Spine	Spine surgeons
Coating	Medical device companies for Licensing Agreements



The ideal bone graft substitute material would be osteoinductive, osteoconductive, resorbable in an predictable manner, biologically acceptable and with a proven safety profile with no adverse local or systemic effects.

Boyan et al. in Laurencin, Cato, Ed: Bone Graft Substitutes, ASTM Int. /AAOS, 2003





Bone grafts substitute Materials

Osteoinductive	Osteoconductive	Osteogenic
DBM ¹	Ceramics	Autografts
BMPs ²	Hydroxyapatite	Allografts
	Deproteinized bone	Xenografts
	Coral-derived products	MSCs ³
	Calcium phosphates	Growth factors
	Calcium sulfates	Cytokines
	Polymer scaffolds	Enamel Matrix Proteins
	Bioglass	Attachment peptides ⁴

¹ Demineralized bone matrix, demineralized freeze-dried bone allografts (DFDBA)

² Bone morphogenic proteins including BMP-2, BMP-4 and BMP-7 (ostegenic protein-1, OP-1)

³ Mesenchymal stem cells, marrow stromal cells and osteoprogenitor cells

⁴ Peptides such as the arg-gly-asp (RGD) sequence in fibronectin, the attachment proteins themselves.



Historie von Calciumsulfat als Knochenersatzmaterial

H. Dreesmann:

Ueber Knochenblombierung.

Beitr. Klin. Chir. 9 (1892) 804.

B. Kovacevic:

Ein Beitrag zum Problem der hämatogenen Osteomyelitis.

Dtsch. Z. Chir. 276 (1953) 432.

L. F. Peltier:

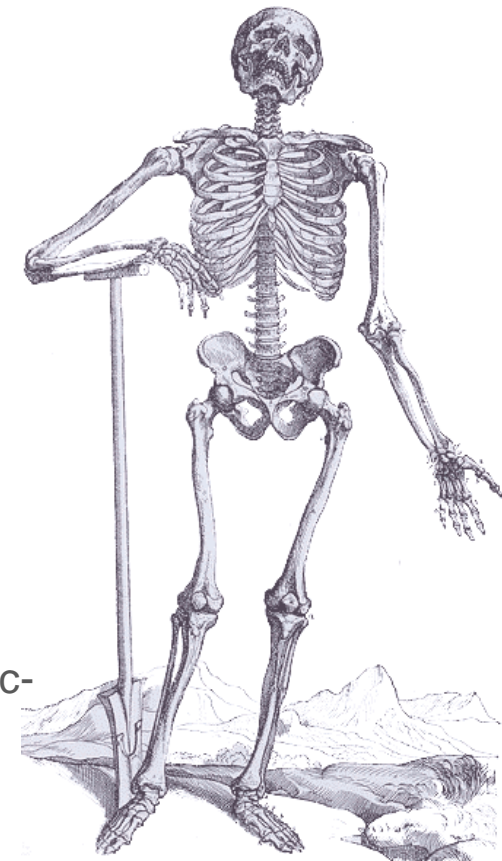
The use of plaster of Paris to fill defects in bone.

Clin. Orthop. 21 (1961) 1.

S. Gitelis, G. T. Brebach:

The treatment of chronic osteomyelitis with a biodegradable antibiotic-impregnated implant.

J. Orth. Surg. 10 (1) (2002) 53-60..





Ziel

- ▶ Entwicklung eines biodegradierbaren Knochenersatzmaterials als Komposit auf Basis von Calciumsulfat
- ▶ Integration einer puffernden Komponente
- ▶ Verwendung eines biodegradierbaren Bindemittels
- ▶ Integration von unterschiedlichen Antibiotika
- ▶ Fertigung bei Raumtemperatur ohne Wasser
- ▶ Sterilisierbarkeit, Lagerfähigkeit



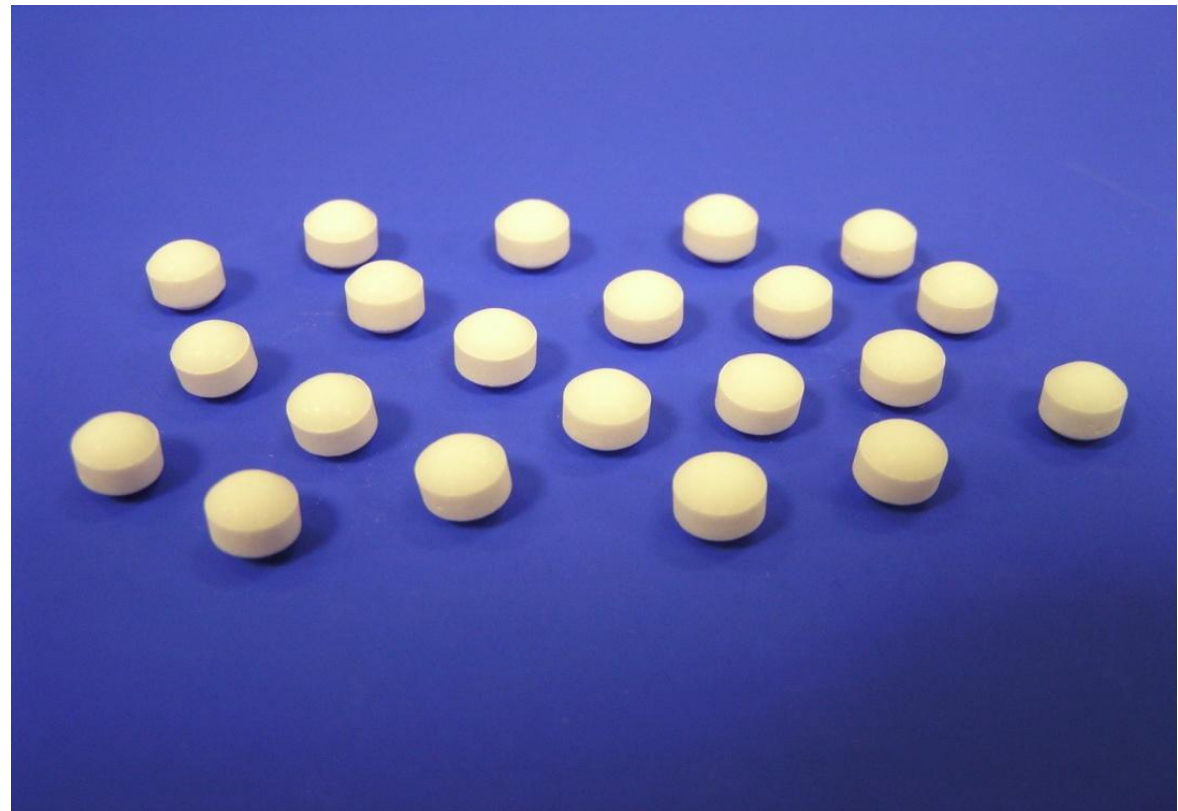
Zusammensetzung pro 1 Herafill® G Formkörper

Bestandteile		
Calciumsulfat- Dihydrat [$\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$]	Ph.Eur.	179.0 mg
Calciumcarbonat [CaCO_3]	Ph.Eur.	45.0 mg
Glycerintripalmitat	In-house	22.0 mg
Gentamicinsulfat [2,5 mg Gentamicinbase]	Ph.Eur.	4.0 mg 1% w/w Gentamicinbase pro Formkörper
Physikalische Eigenschaften		
1 Formkörper		250.0 mg
Mechanische Stabilität		> 100 N
Röntgendicht		



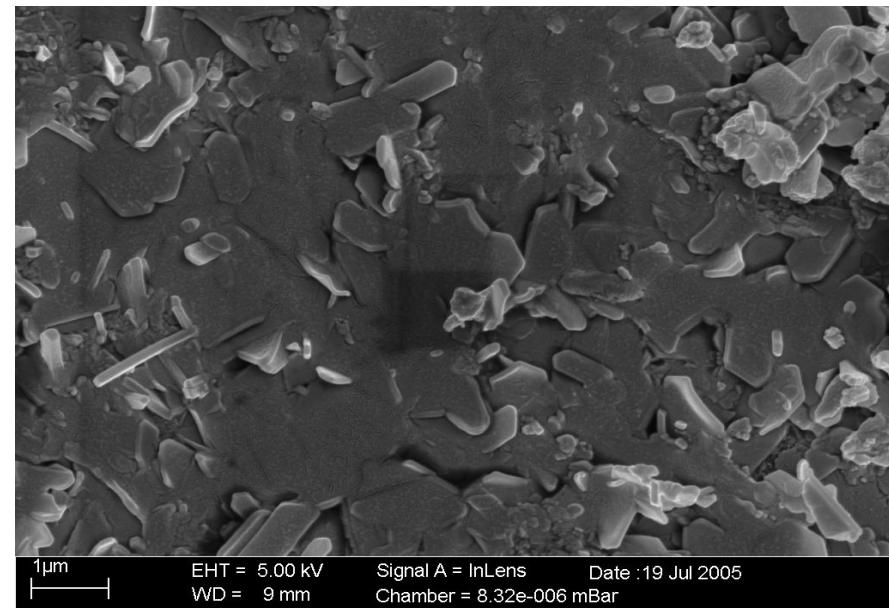
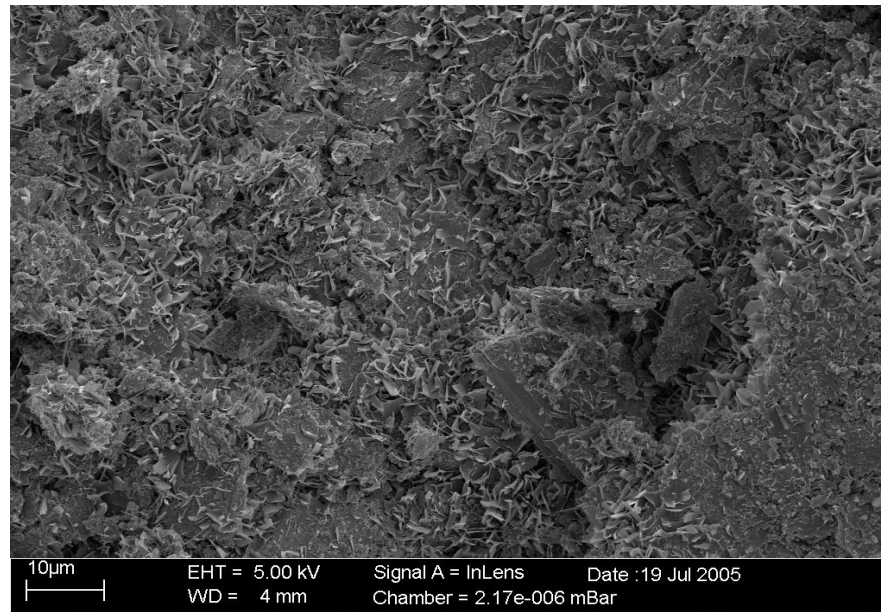
Heracell®

- Zylindrisch-bikonvex
- Durchmesser: 6 mm
- Höhe: 6mm
- 40 Formk.: 10 ml Vol.
- 20 Formk.: 5 ml Vol.
- Y- Sterilisation





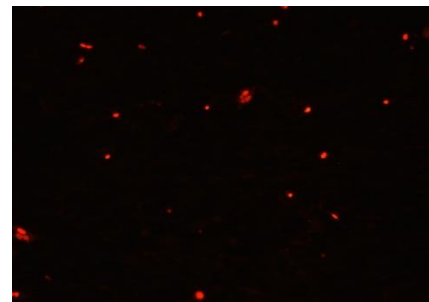
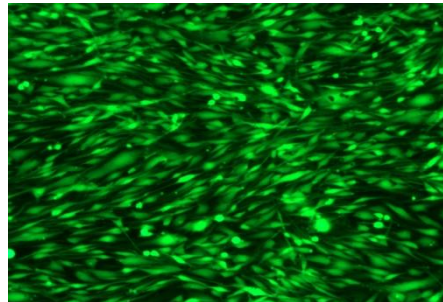
REM-Aufnahme Oberfläche



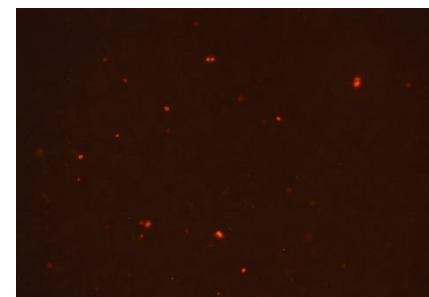
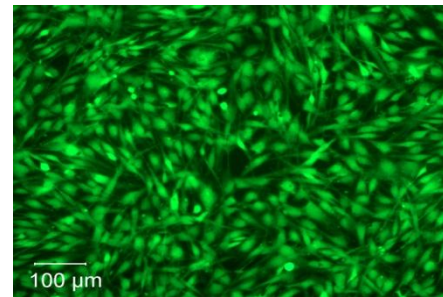


In vitro-Cytotoxizitätsuntersuchungen

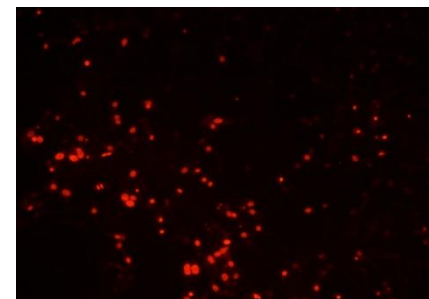
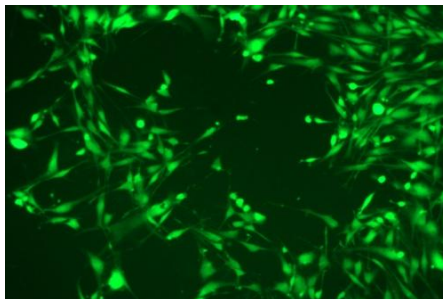
ohne Wirkstoff



mit Gentamicin



mit Vancomycin

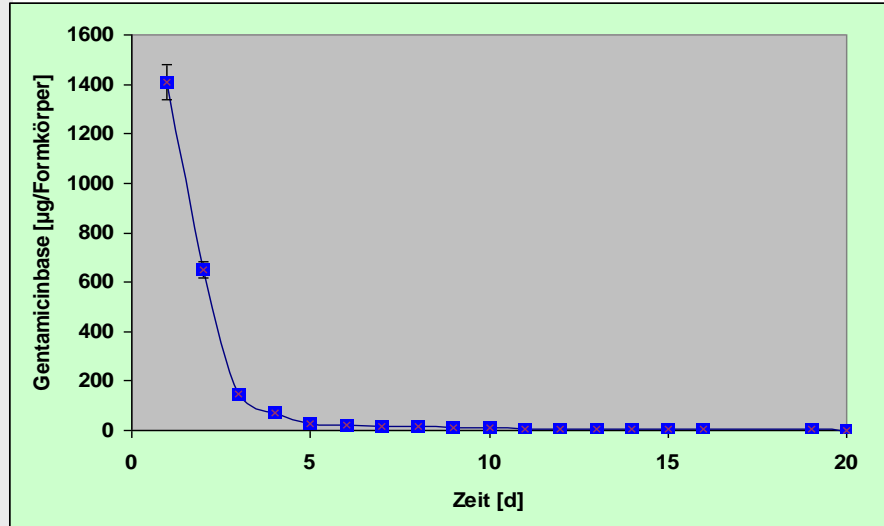


MC3T3-E1-Zellen
Färbung:
Fluoresceindiacetat/Ethidium-
bromid

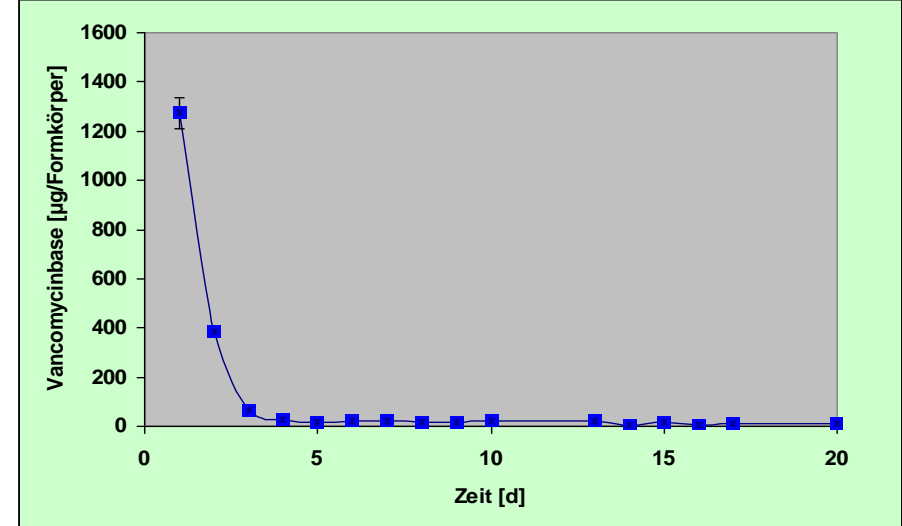


Antibiotikafreisetzung pro Formkörper

Gentamicin



Vancomycin





Gentamicinfreisetzung in vitro

Freisetzungsbedingungen / Analysemethoden

Es wurden 6 Herafill® G-Formkörper in PBS-Puffer (pH 7,4) bei 37°C gelagert. Täglich wurden 20 ml Medium entnommen und durch 20 ml frischen PBS-Puffer ersetzt. Die Bestimmung des freigesetzten Gentamicins erfolgte mit einem TDX-Analyser der Fa. Abbott.

Parameter der Herafill® G-Formkörper:

Masse: 250 mg

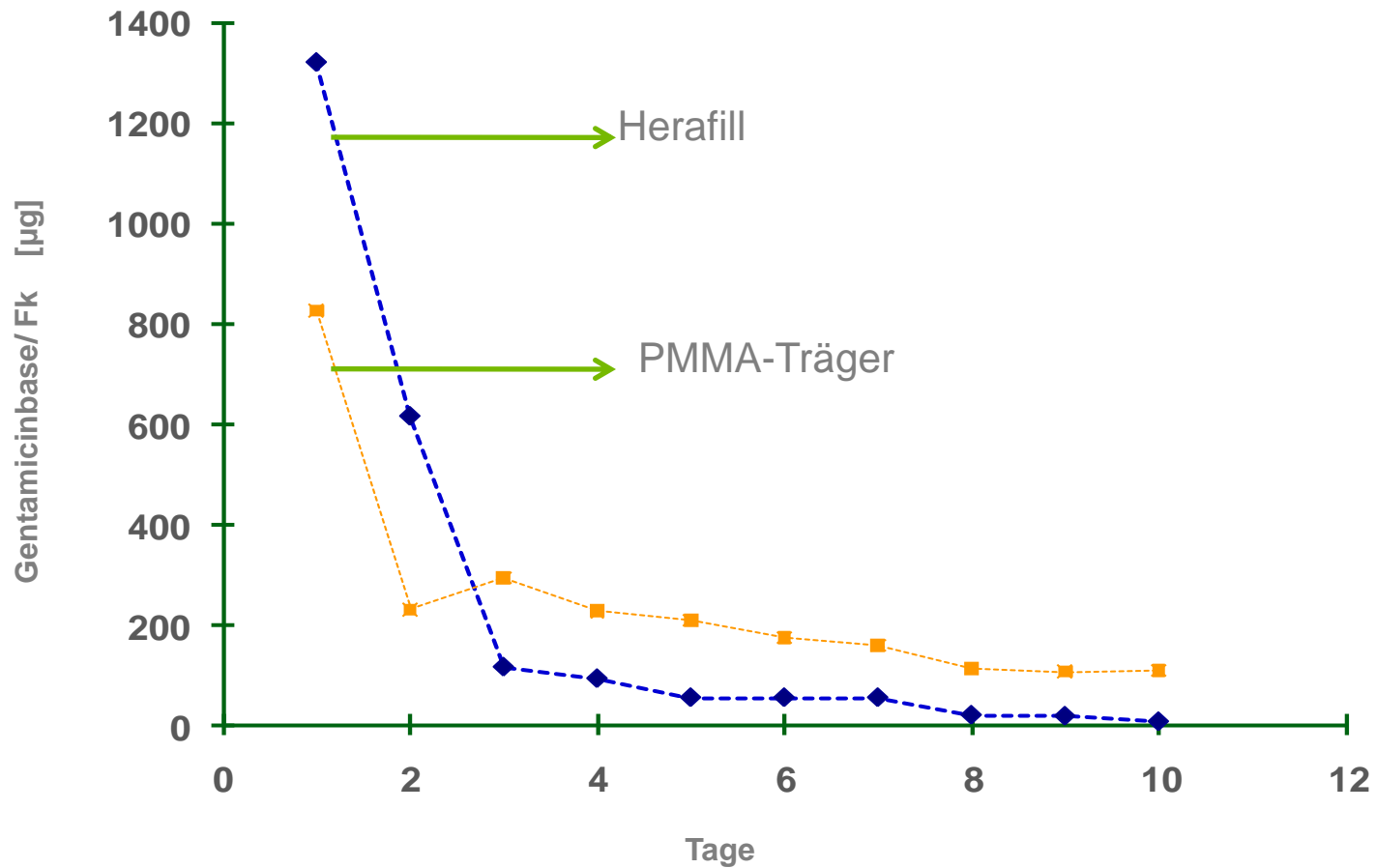
Gentamicinbasegehalt: 1 Ma%

Durchmesser: 6 mm

Höhe: 6 mm



Gentamicinfreisetzung Herafill® G Beads vs. PMMA-Träger





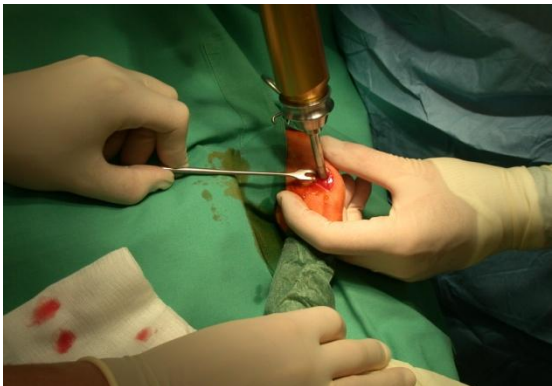
Herafill® G Beads

In vivo-Untersuchungen zum Resorptionsverhalten



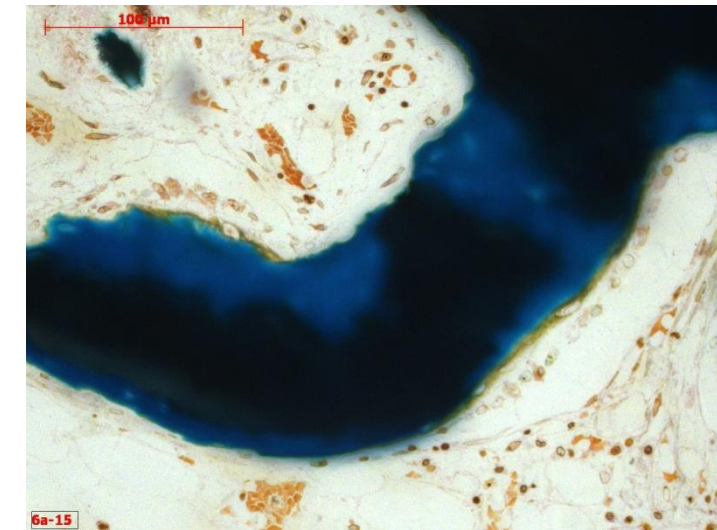
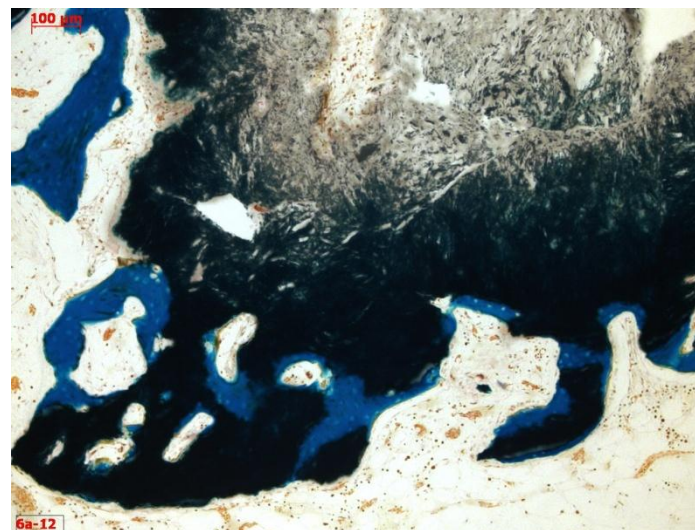
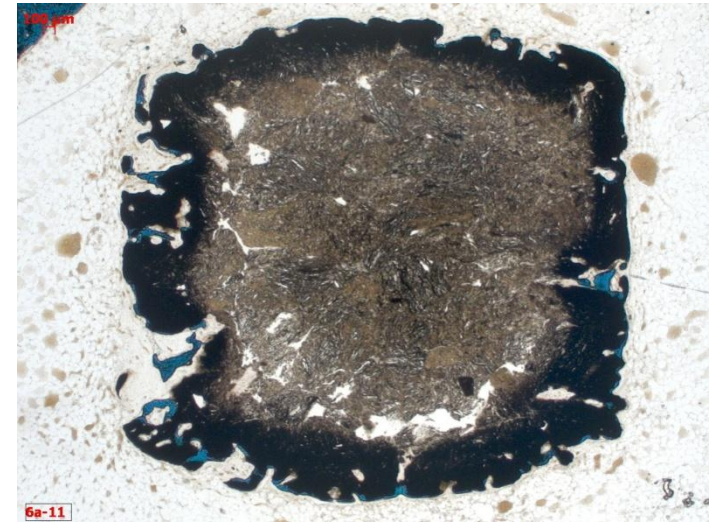
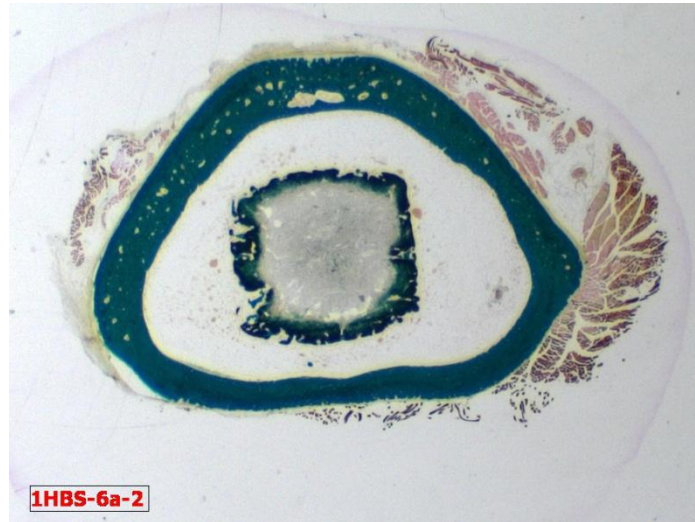
Implantationstudien

- ▶ 2 Studien, Studie 1 Oblong-Formkörper, Studie 2 Herafill-Formkörper
- ▶ Tierart: Kanninchen, „Weiße Neuseeländer“, weiblich
- ▶ Durchschnittsgewicht: 4,5 kg
- ▶ Anästhesie: intramuskulär Medetomidin 0,25 mg/kg und Ketamin 17 mg/kg
- ▶ Implantationsort: Femur (Studie 1),Tibia distal (Studie 2)



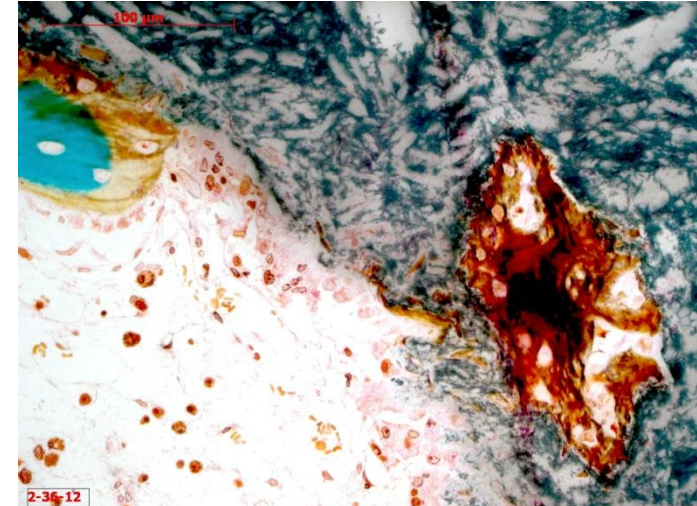
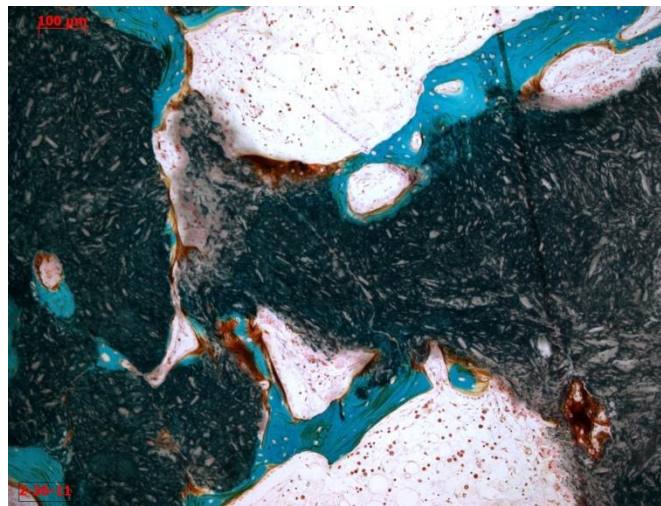
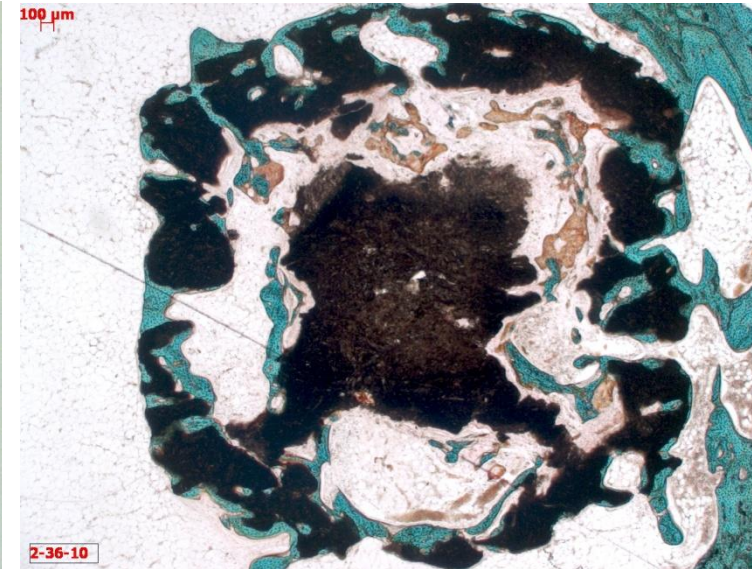
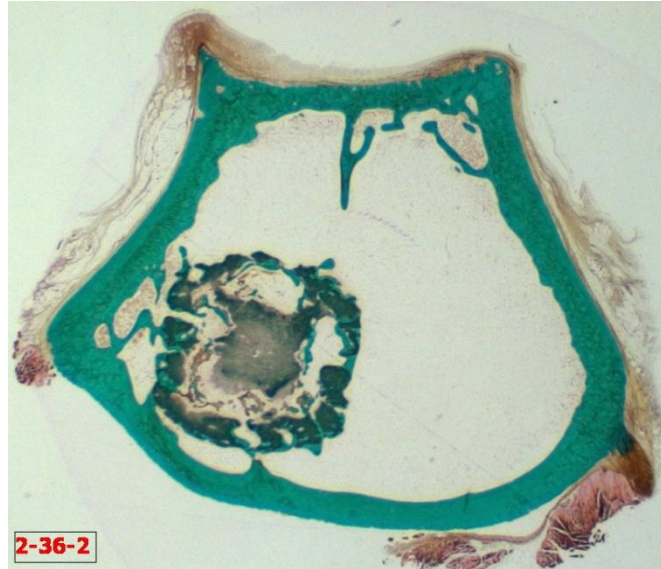
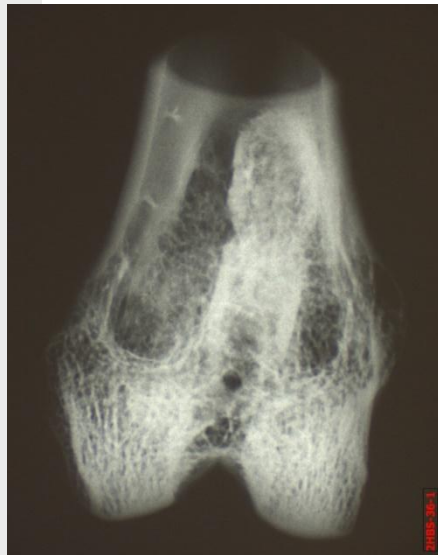


Präparat 6;
6 Wochen po.



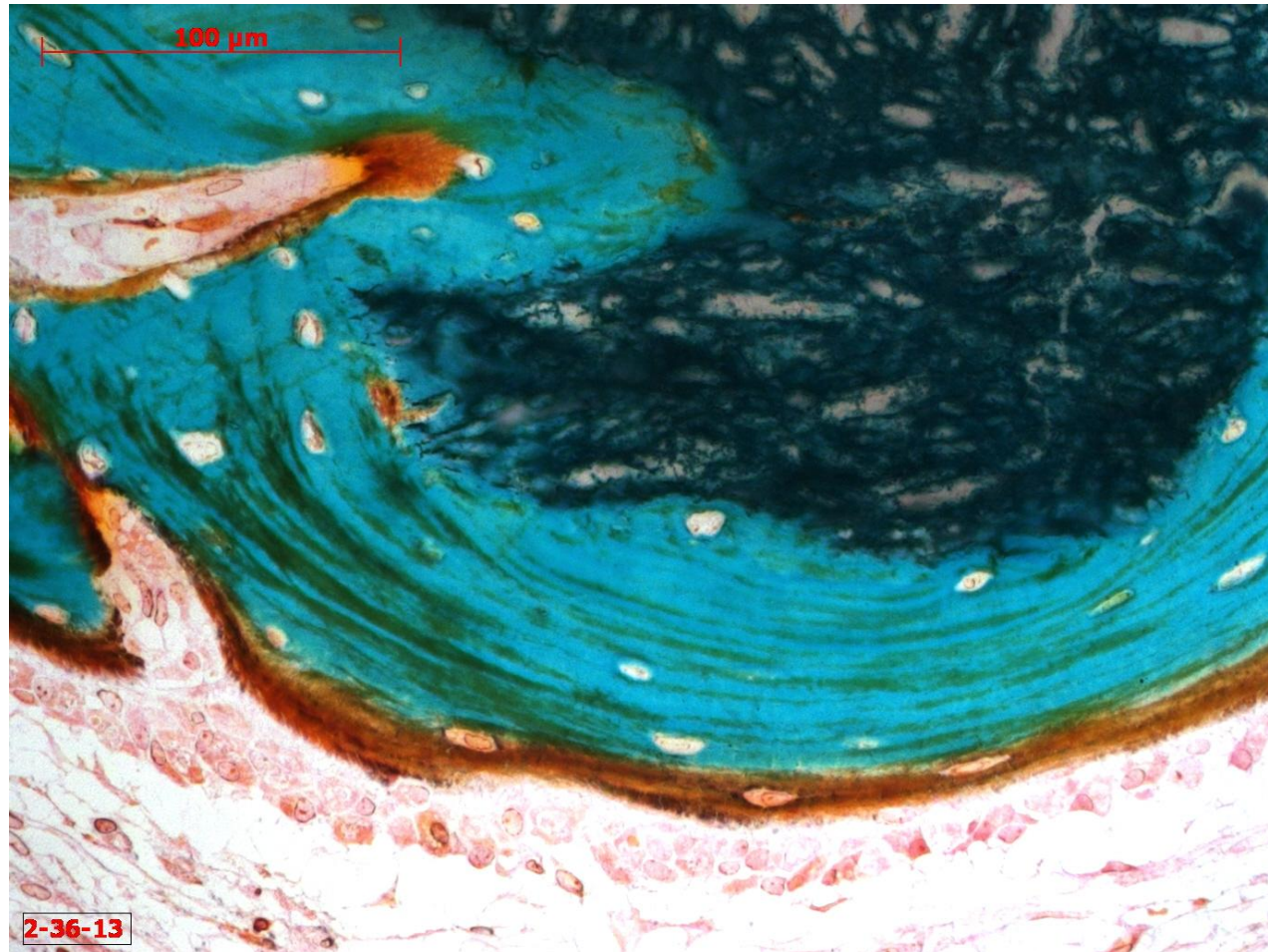


Präparat 36;
12 Wochen po.



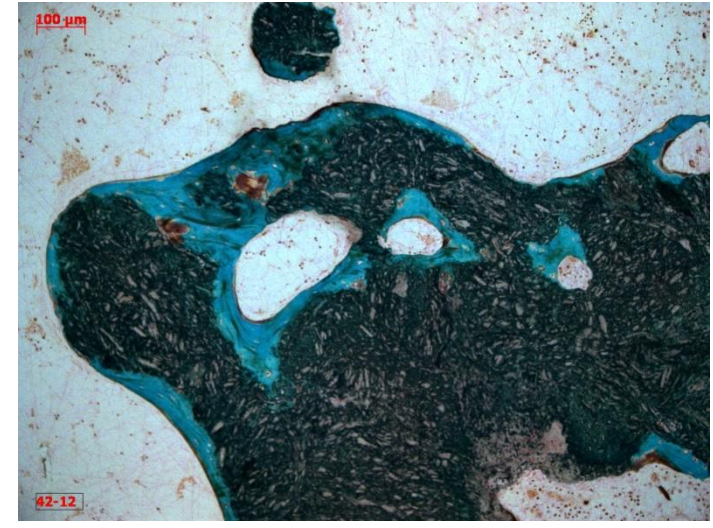
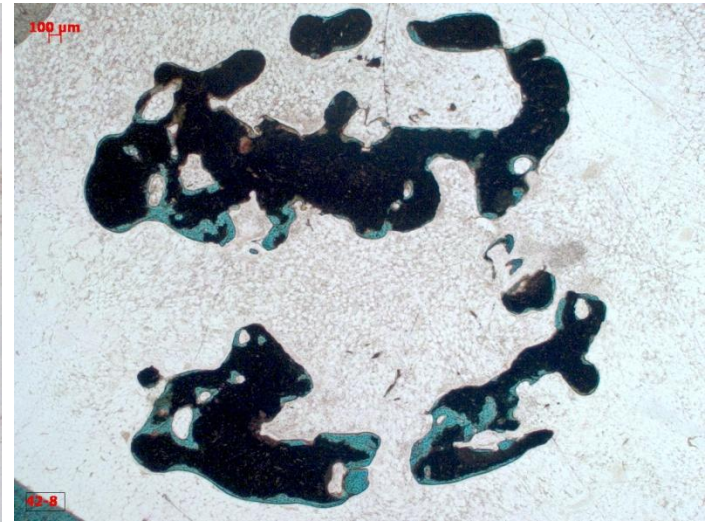
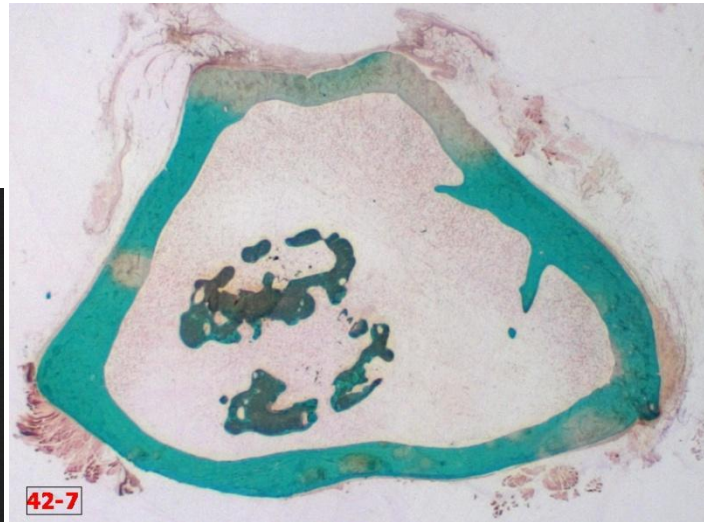


Histologie / 12 Wochen nach Implantation





Präparat 42;
24 Wochen po.





Herafill[®] G Beads

μ-Computertomographie



μ-Computertomographie – Schnittebenen

proximal

Tuberositas tibiae

sagittale Ebene

transversale Ebene

Tibia

Ulna

medial

distal

lateral

medial

lateral

Tiernummer

108

2

2

Sagittal Plane

Coronal Plane

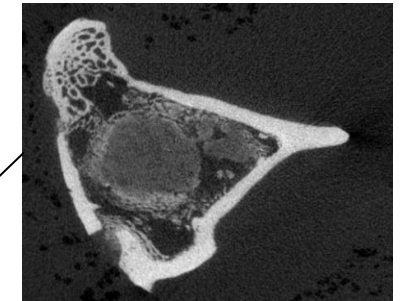
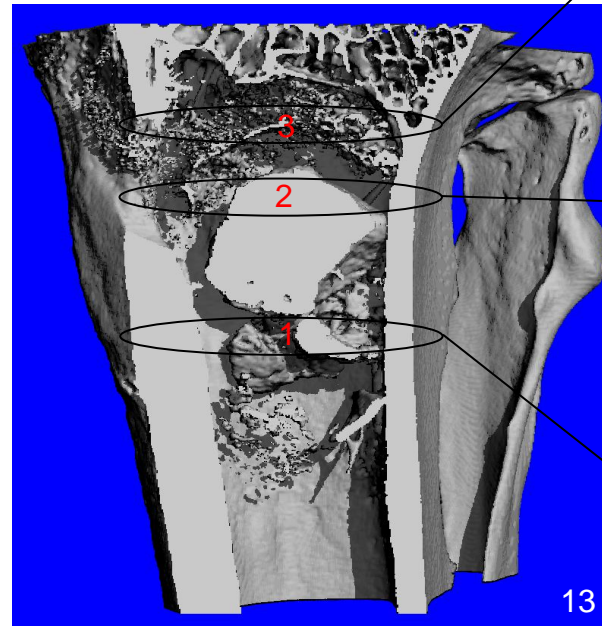
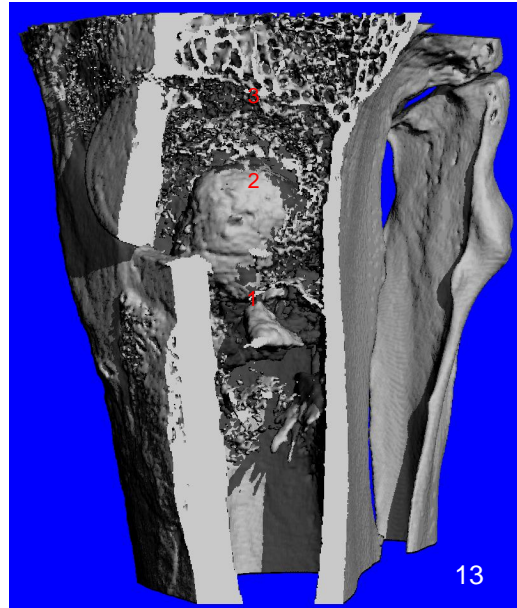
Transverse Plane

Body Planes

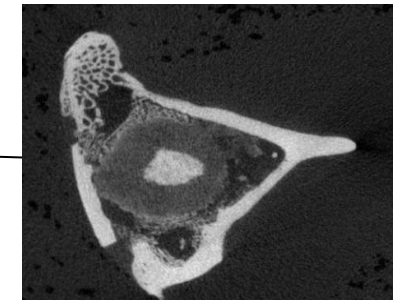
Detailed description: The main image is a 3D μ-CT scan of a tibia and ulna. The tibia is on the left, and the ulna is on the right. The proximal end is at the top, and the distal end is at the bottom. The tuberositas tibiae is labeled at the top of the tibia. A grid of horizontal lines is shown on the proximal end. Two inset images show cross-sections: a sagittal plane (top right) and a transverse plane (bottom right). The transverse plane shows a cross-section of the tibia with a central medullary canal. A diagram on the bottom right shows a human figure with three planes: Sagittal Plane, Coronal Plane, and Transverse Plane. The number 108 is at the bottom right of the main image, and the number 2 is in the bottom right of both inset images. The word 'Tibia' is on the left, and 'Ulna' is at the bottom. 'medial' and 'lateral' are labeled at the bottom. 'Tiernummer' is at the bottom right.



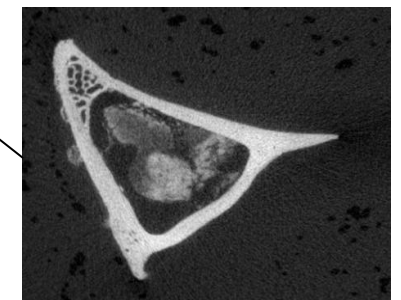
4 Wochen p. op / Präparat 13



13-440



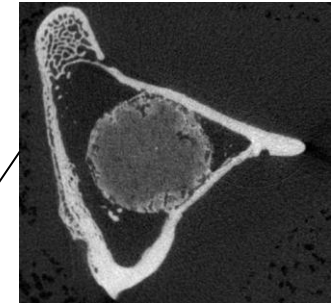
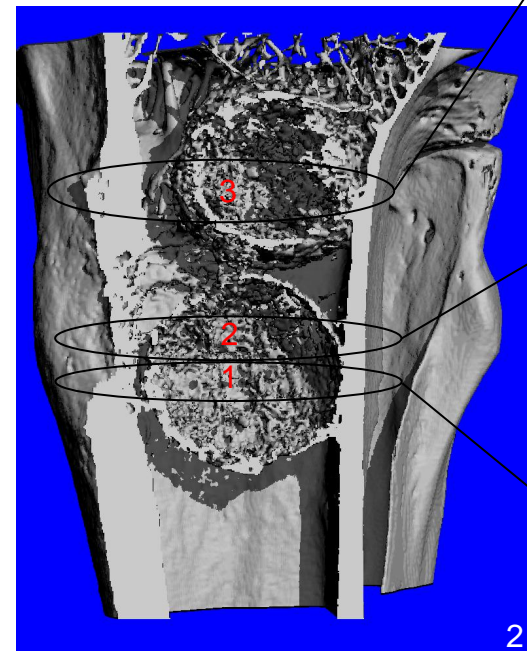
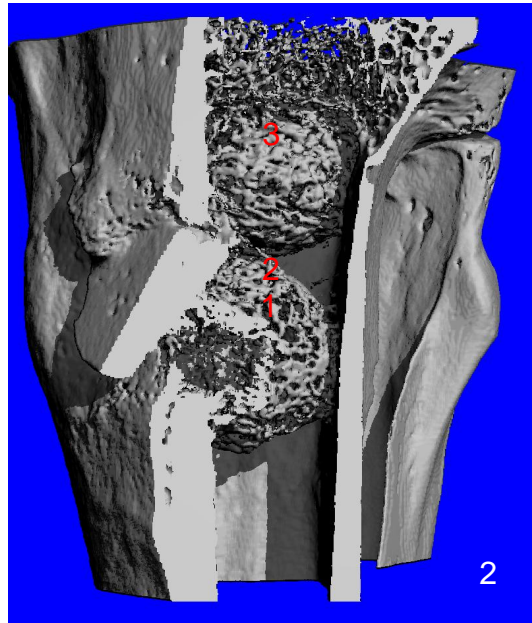
13-420



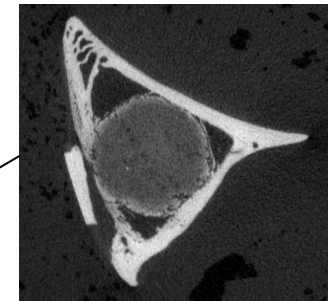
13-300



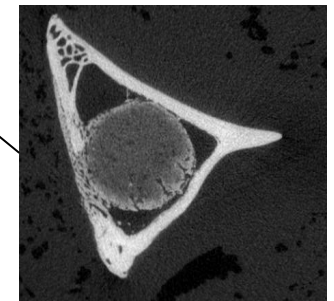
6 Wochen p. op / Präparat 2



2-390



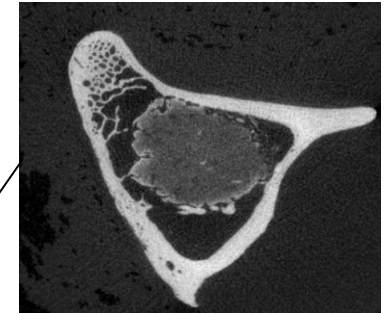
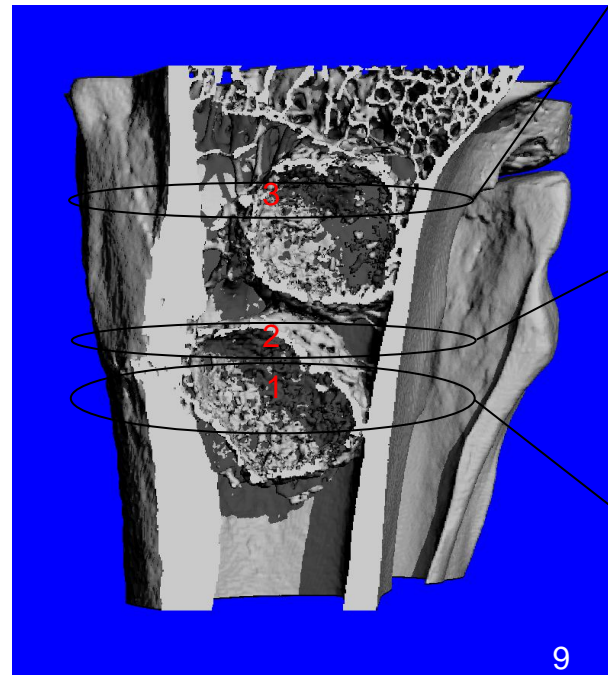
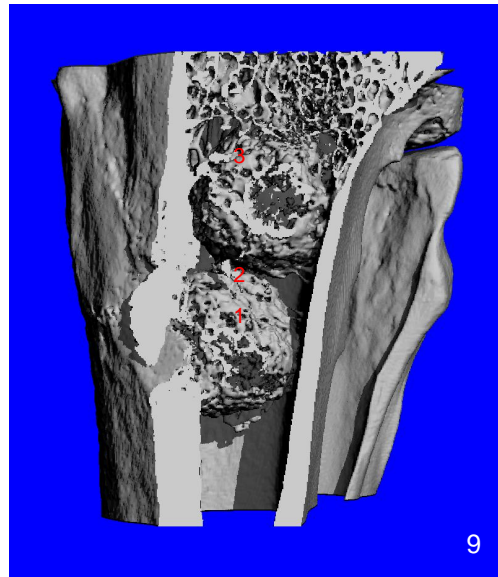
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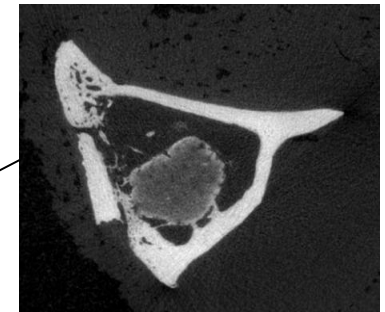
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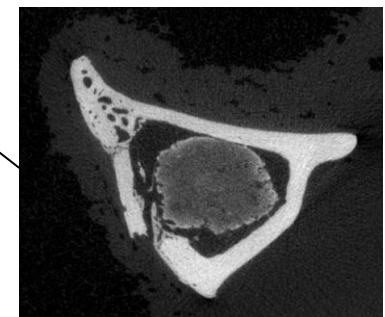
8 Wochen p. op / Präparat 9



9-380



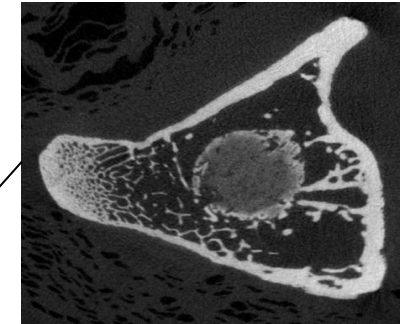
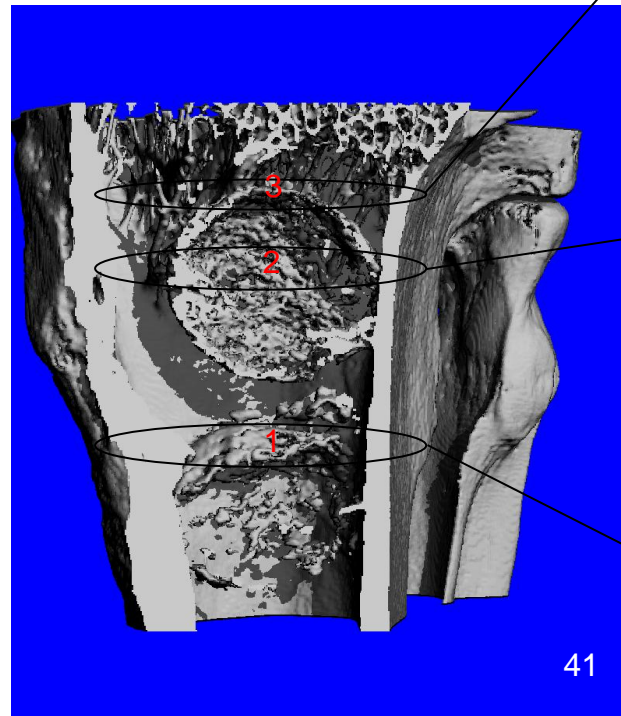
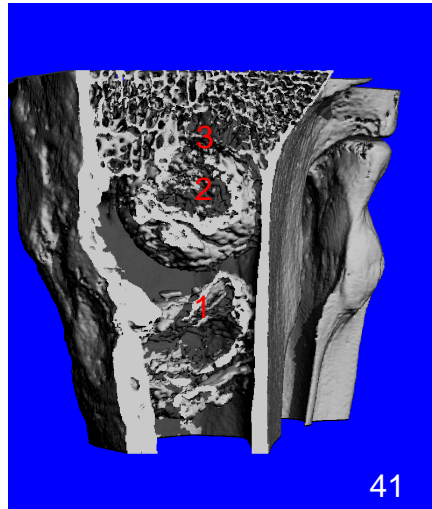
9-270



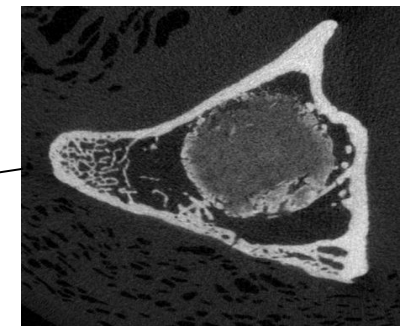
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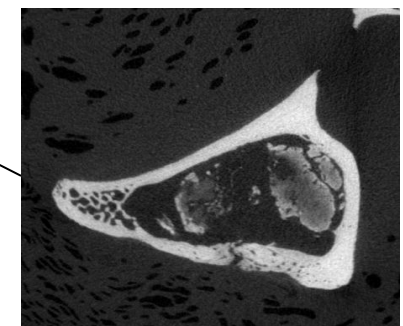
12 Wochen p. op / Präparat 41



41-370



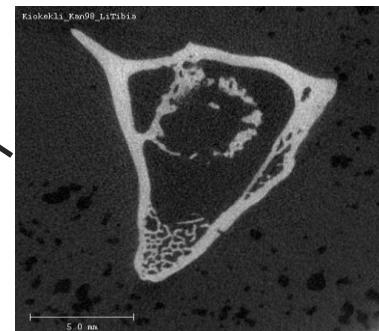
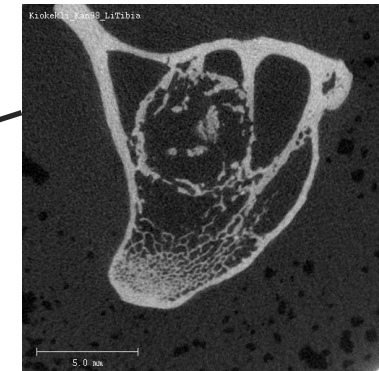
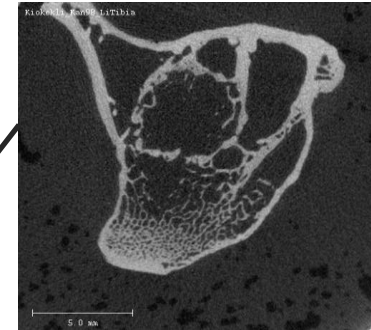
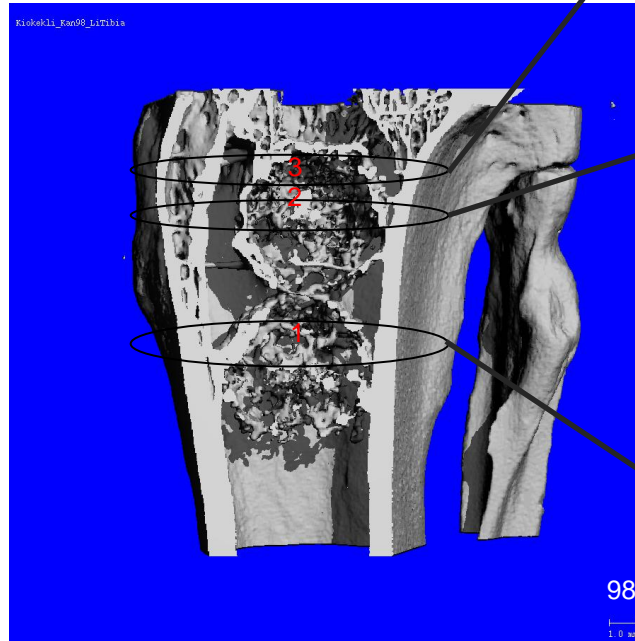
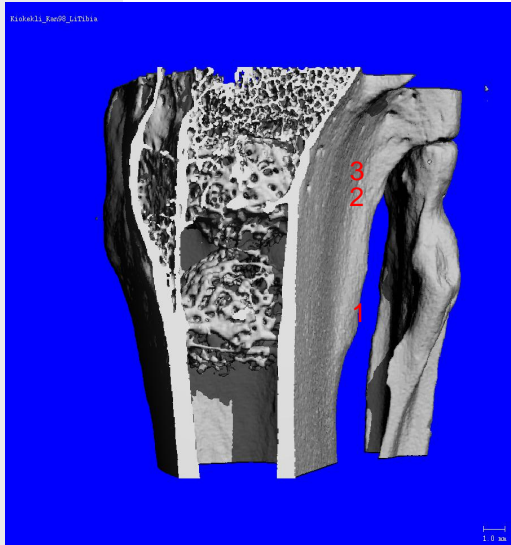
41-310



41-160

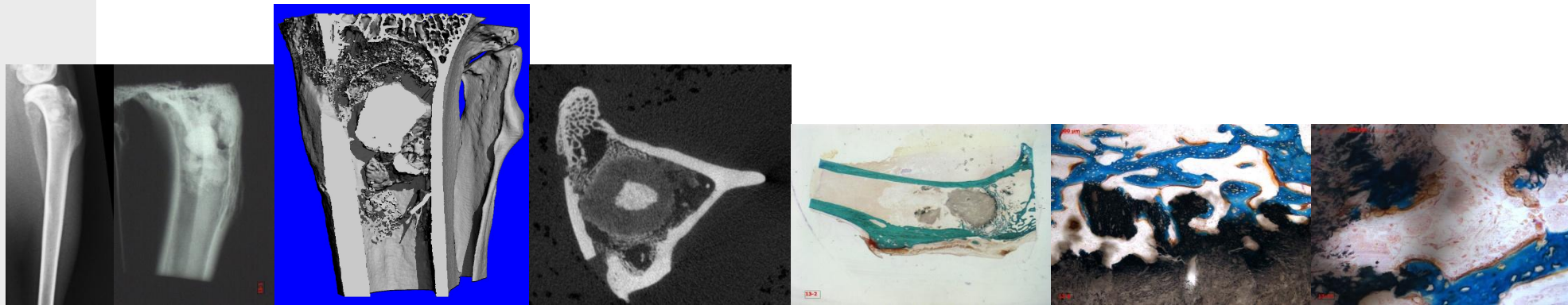


24 Wochen p. op / Präparat 98

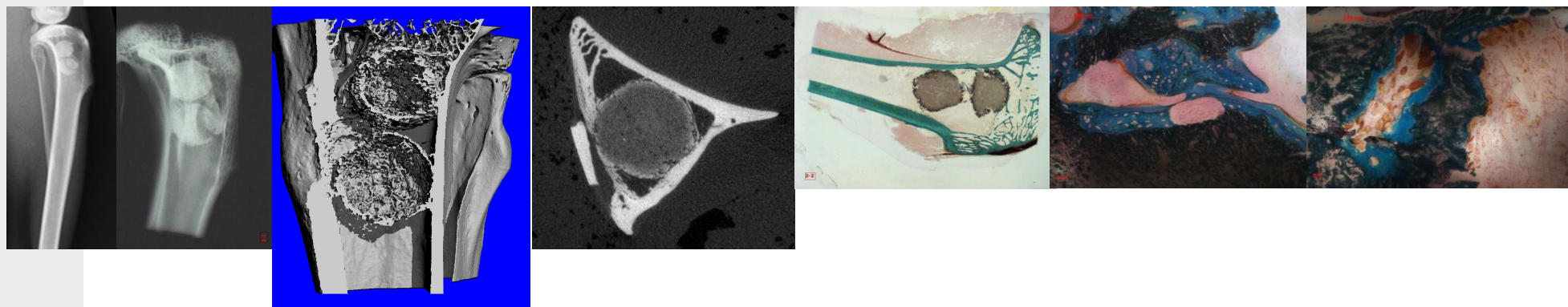




4 Wochen / Präparat 13

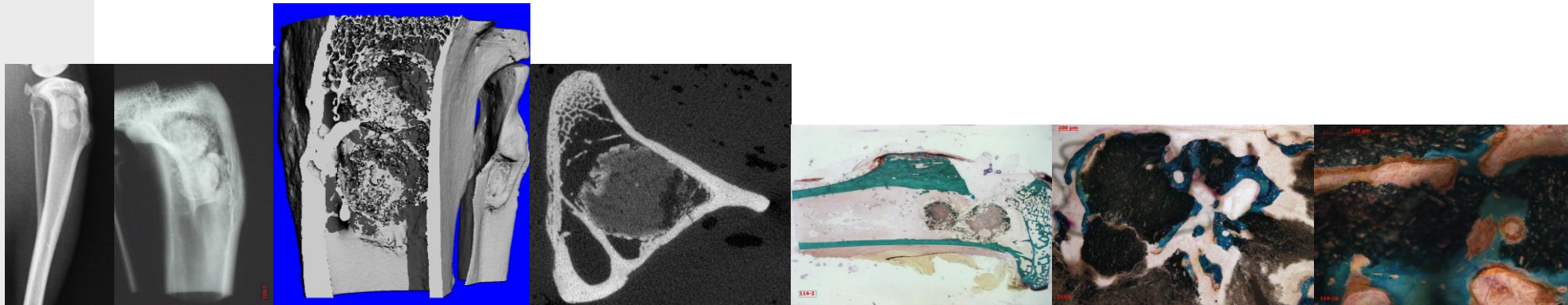


6 Wochen / Präparat 2

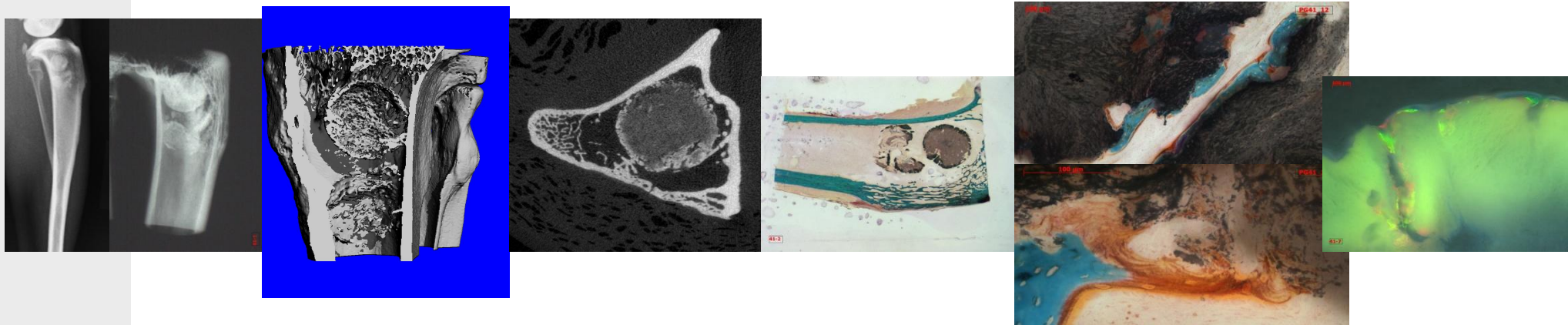




8 Wochen / Präparat 114



12 Wochen / Präparat 41





Herafill[®] G Beads

Human Pharmakokinetik und erste klinische Fälle



Studienziel:

Bestimmung der Gentamicinkonzentration in Blutserum, Urin und Wundsekret von Patienten nach Implantation des Knochenersatzmaterials Herafill® in vormals infizierten chirurgische sanierten Knochendefekte

Hauptziele:

- Bestimmung der Gentamicinkonzentration in Blutserum, Wundsekret und Urin
- Wundheilung
- Reinfektion
- Laborparameter zur Beurteilung der Sicherheit

Design:

Offen, unkontrolliert, nicht-randomisiert, monozentrisch

Patientenzahl:

n=20

Einschlusskriterien:

Patienten mit post-traumatischer/post-operativer Knocheninfektion der oberen oder unteren Extremitäten verursacht durch Gentamicin-empfindliche Keime

Defektgröße: 10 - 50 ml



Table A: STUDY SCHEDULE

Time	Day -3 to 0	Day 0 within -6 hrs	Day 0	Day 0	Day 1	Day 2-21	Month 3	Month 6
	Screening	Pre-surgical	Surgery	Post-surgical ¹	Post-surgical ¹	Post-surgical ¹	Follow-up	Follow-up
Patient's eligibility, written consent	X							
Laboratory tests for checking eligibility	X							
Medical history/concomitant medication	X							
Clinical safety laboratory ²		X			24 h	Day 2, 4, 6, 10, 14		
Laboratory parameters indicative for infections ³		X			24 h	Day 2, 4, 6, 10, 14, 21		
Microbiological sampling			X					
Implantation of PalaSorb [®] G			X					
Blood serum sampling for gentamicin analysis		X			2, 4, 6, 10 h	24 h	Day 2, 3, 4, 5, 6, 7	
Wound secretion sampling for gentamicin analysis			X ⁴		2, 4, 6, 10 h	24 h	Day 2, 3	
24 h urine collection for gentamicin analysis		X			10 h	24 h	Day 2, 3, 4, 5, 6, 7	
Evaluation of wound healing							Day 2, 4, 6, 8, 10, 12, Y ⁵	
Evaluation of implant							variable ⁶	X ⁷
Clinical Outcome								X ⁸
Adverse event monitoring ⁹	X	X	X	X	X	X	X	

1) Time points after finalization of suture

2) Serum creatinine, urea, total bilirubine, GGT, GPT, GOT

3) CRP, leucocytes

4) Intra-operative, before surgical debridement and implantation of study material

5) Y = day of removal of sutures.

6) Most likely between days 2-4. Depending on the time point a post-surgical X-ray is indicated/performed.

7) Depending on the availability of clinically indicated X-ray images.

8) To be obtained at Month 6 visit, or at any timepoint of early termination.

9) From the time of signed Informed Consent up to Day 21. Only postdose events occurring from implantation on will be classified as adverse events through data analysis.



Gentamicinanalytik

Quantitative Bestimmung von Gentamicin in Humanplasma, Wundsekret u. Urin

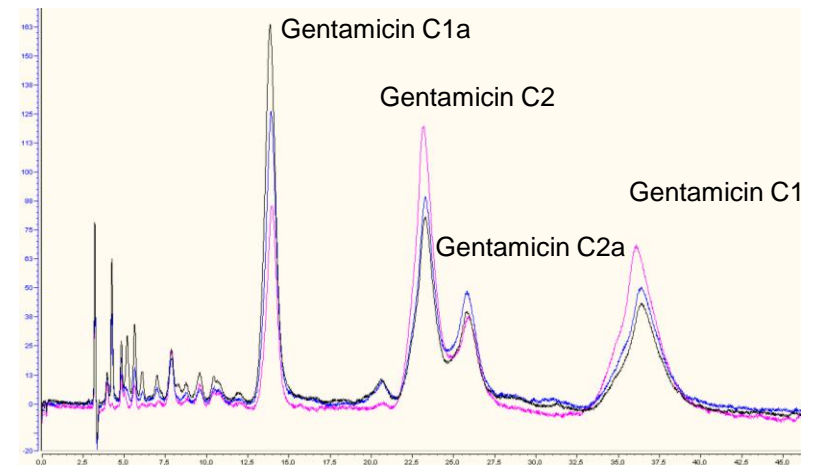
Messprinzip und Grundlagen:

Proteinfällung (nur Plasma u. Wundsekret)

Extraktion der vier Gentamicin-Verbindungen C1, C2, C2a und C1a sowie des internen Standards (Tobramycinsulfat);

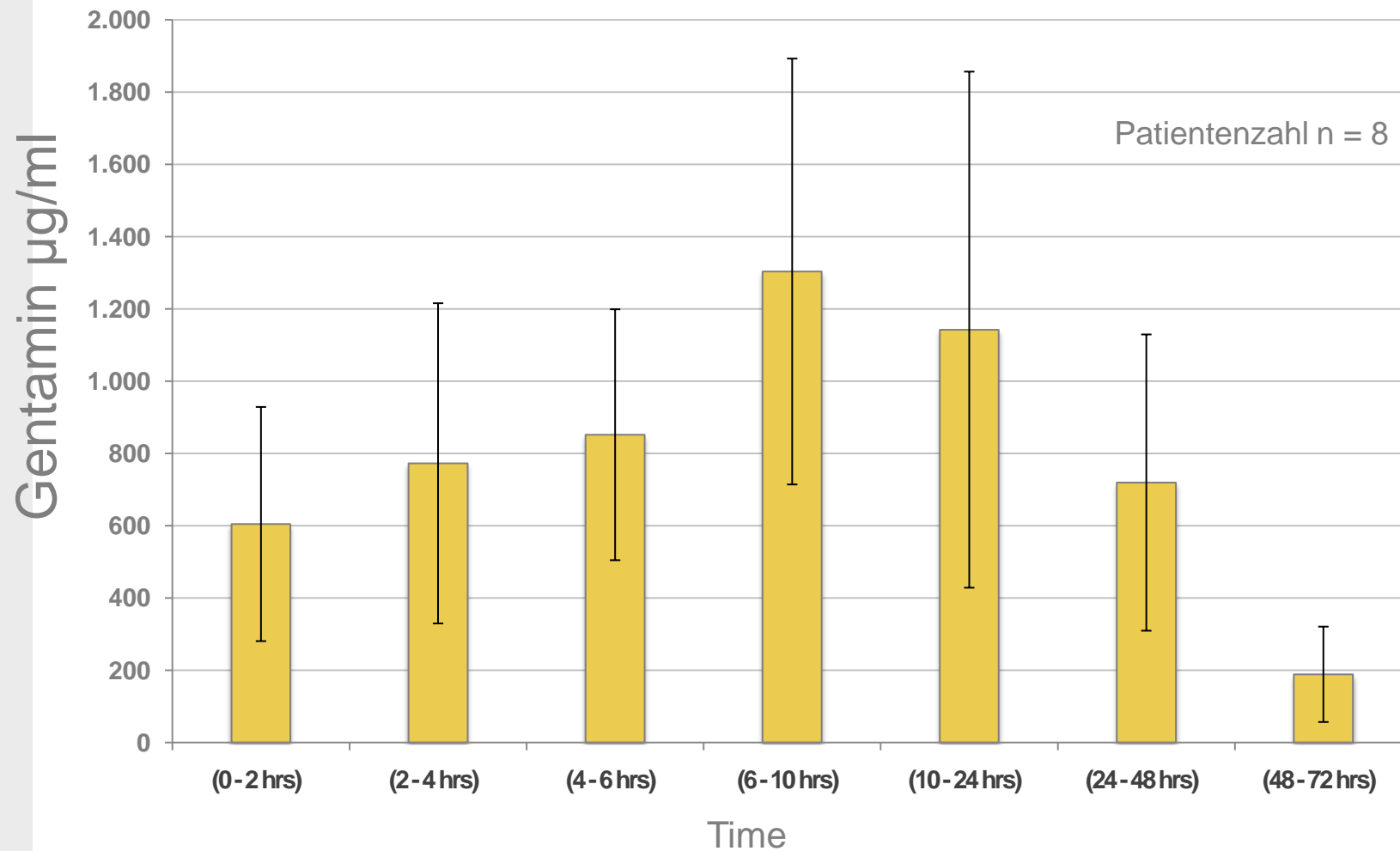
HPLC-Trennung; Detektion mit einem Hochleistungshybrid-Massenspektrometer

Kalibrierbereich: 1-750 ng/mL (Linearity) bei Plasma u.
Wundsekret
2-250 ng/mL (Linearity) bei Urin



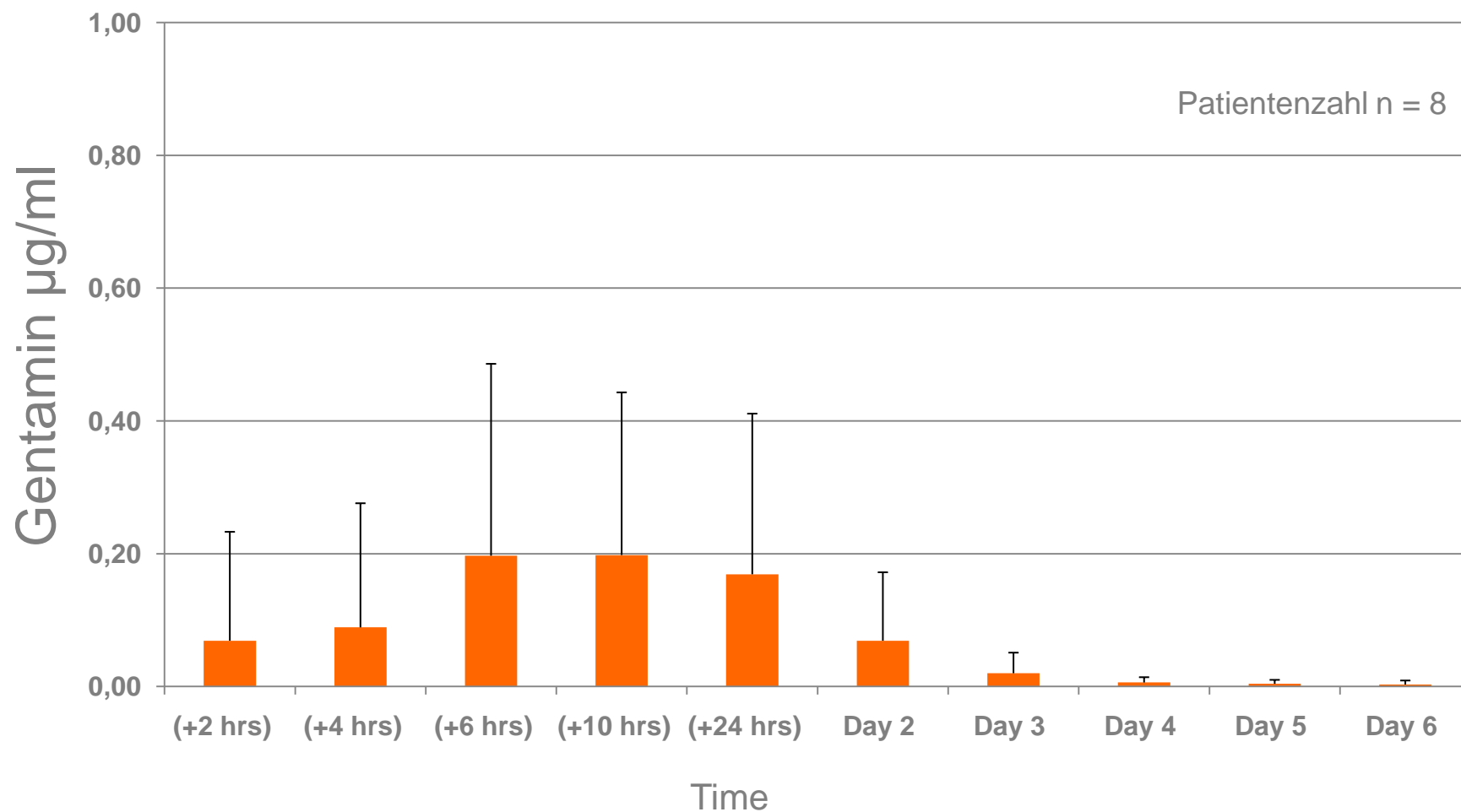


Gentamicinkonzentration im Wundsekret



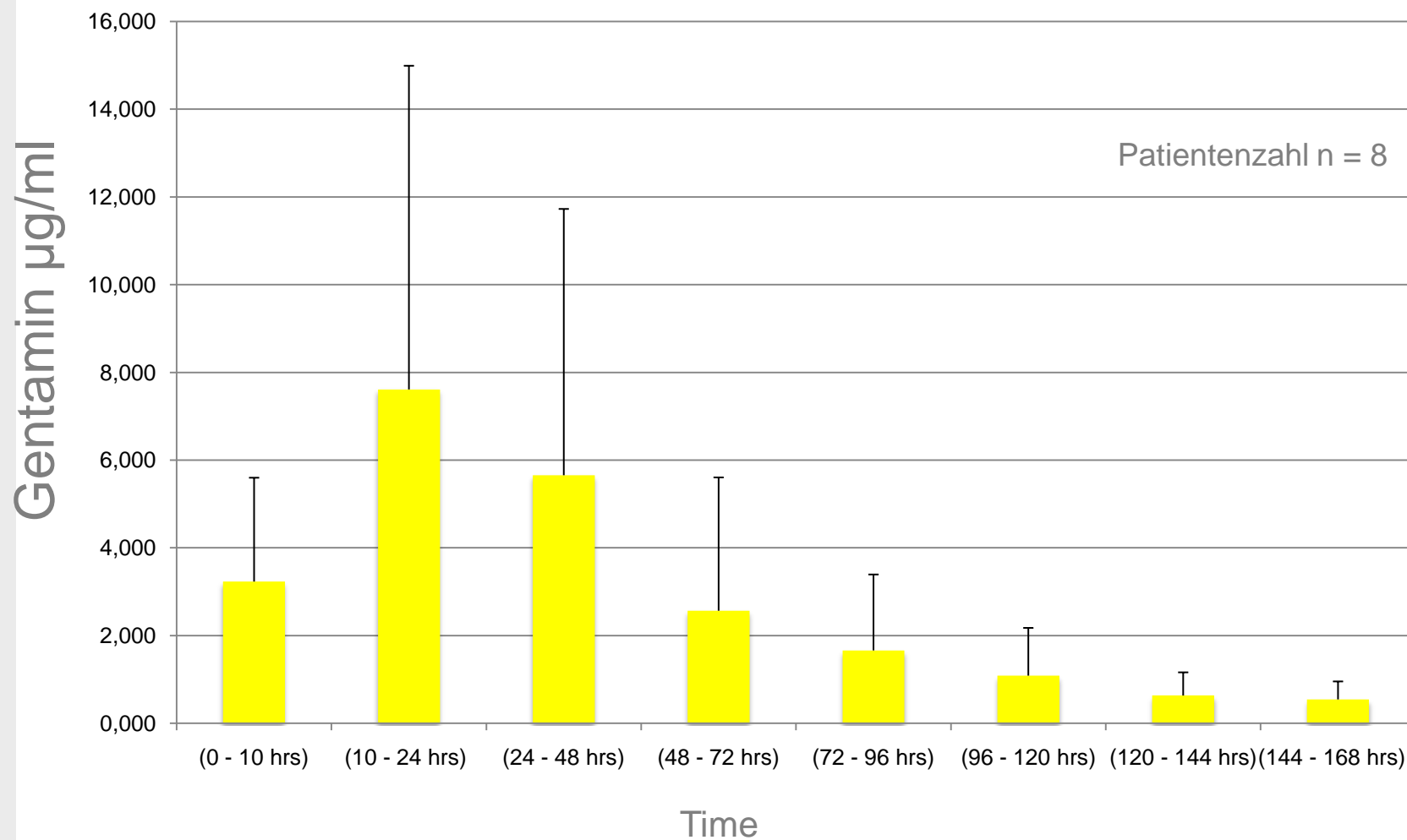


Gentamicinkonzentration im Blutserum





Gentamicinkonzentration im Urin



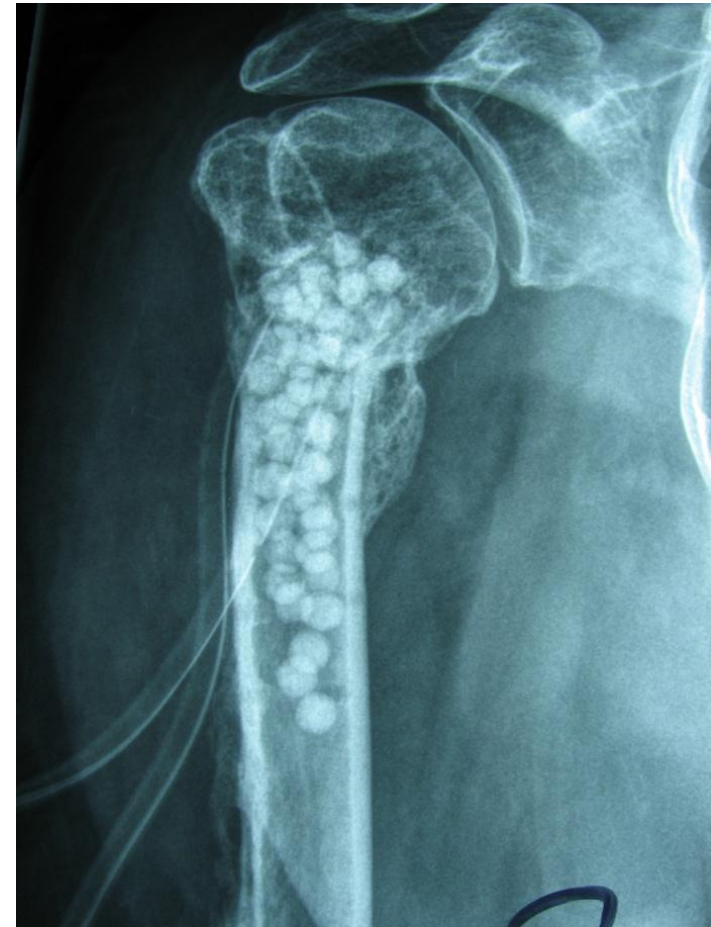


Patient 8

prä-op.



post-op.



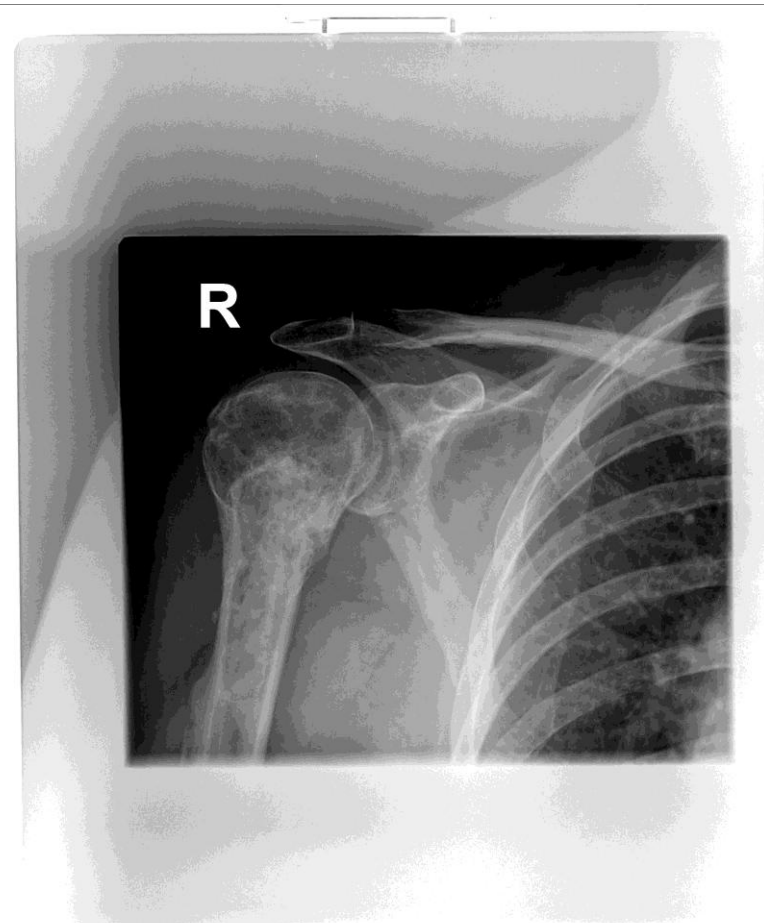


Patient 8

3 Monate



6 Monate





Patient 5

post-op





Patient 5

3 Monate





Patient 5

6 Monate





Patient 10

prä-op.

post-op.

3 Monate





Zusammenfassung der Ergebnisse zu Herafill®

- Protrahierte Wirkstofffreisetzung über max.10 Tage (in vitro)
- Sehr gut resorbierbar
- Zellvermittelte Degradation
- Sehr gute Gewebeverträglichkeit
- Wirksamer Schutz des Implantationsgebiets
- Geringe systemische AB-Spiegel



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Vielen Dank !