Abschlußbericht

Studientitel:

TRANSLATIONAL THERAPY IN PATIENTS WITH OSTEOGENESIS IMPERFECTA

–

A PILOT TRIAL ON TREATMENT WITH THE RANKL-ANTIBODY DENOSUMAB

Prüfsubstanz:

Denosumab (Prolia®) RANKL-Antibody (60MG/ML)

Eudra-CT Nummer:

2012-002887-29

Sponsornummer:

Uni-Koeln-1574

Register-Nummer:

DRKS number: 00004521

Kurzbezeichnung:

(OI-AK)

Version:

0.2 VOM 09.10.2015

Sponsor der klinischen Prüfung:

UNIVERSITÄT ZU KÖLN

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Studienbeginn – Studienabschluss:

04. JULI 2013 – 26. JANUAR 2015

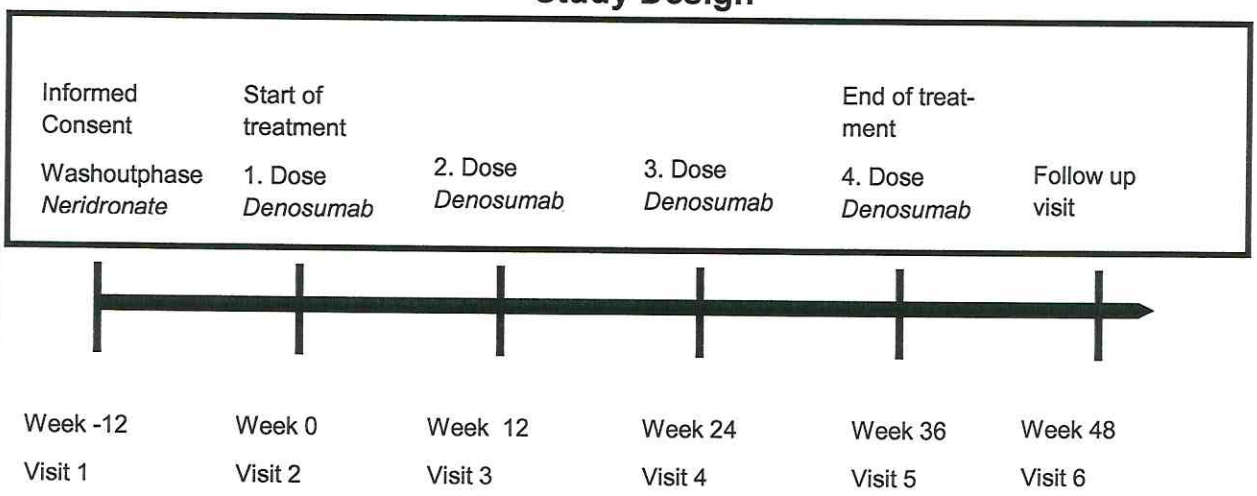
Titel der Studie	Translational therapy in patients with Osteogenesis imperfecta - a pilot trial on treatment with the RANKL-antibody denosumab Translationale Therapie bei Patienten mit Osteogenesis imperfecta - Pilotstudie zur RANKL-Antikörpertherapie mit denosumab **PEI Vorlage-nummer: 1760/01**
Art des Vorhabens	Clinical trial phase II (Arzneimittelgesetz)
Diagnose	Osteogenesis imperfecta (OI)
Sponsor / Vertreter	Universität zu Köln Albertus-Magnus-Platz 50923 Köln Represented by: Priv.-Doz. Dr. med. Oliver Semler Klinik und Poliklinik für Kinder- und Jugendmedizin Uniklinik Köln Kerpener Str. 62 50937 Köln Joerg.semler@uk-koeln.de
Leiter der klinischen Prüfung / Prüfärzte	Priv.-Doz. Dr. med. Oliver Semler Klinik und Poliklinik für Kinder- und Jugendmedizin Uniklinik Köln Kerpener Str. 62 50937 Köln Joerg.semler@uk-koeln.de Dr. med. Heike-Katharina Hoyer-Kuhn Prof. Dr. med. Eckhard Schönau Klinik und Poliklinik für Kinder- und Jugendmedizin Uniklinik Köln Kerpener Str. 62 50937 Köln

Hauptprüfer in verschiedenen Zentren	Not applicable
Studienzentren:	Klinik und Poliklinik für Kinder- und Jugendmedizin Uniklinik Köln Kerpener Str. 62 50937 Köln
Veröffentlichung der Studie (Reference)	The manuscript is still under review. It was submitted in the end of June 2015.
Studienzeitraum	04.07.2013 – 26.01.2015
Studienziele	Osteogenesis imperfecta (OI) is a rare disease leading to bone fragility. Many genes are known to perturb formation and processing of collagen leading to a disturbed function of osteoblasts and osteoclasts. Denosumab as a RANK ligand antibody inhibiting osteoclast maturation has been approved for osteoporosis treatment in adults. Almost no data about its use in children or in OI are available. We investigated efficacy and safety aspects after a 48 week treatment course with denosumab in a phase-II- trial.
Primärer Zielparameter	This pilot study aims to assess the safety and efficacy of a therapy with the RANKL-antibody denosumab in children 5-10 years of age with OI with mutation in COL1A1 or COL1A2. As primary endpoint we use bone density of the lumbar spine, which is a well-accepted standard for a treatment with antiresorptive drugs. The efficacy will be assessed by DXA measurements at the lumbar spine. The measurements will be scheduled in a way that they will be done during the routinely done yearly assessments.
Sekundäre Zielparameter	• Safety will be assessed by laboratory tests and by analyzing AEs/SAEs. • A decrease of osteoclastic activity measured by Deoxypyridinolin (DPD) and changes of bone metabolism (Parathor-

	mone, N-Telopeptides, Osteocalcin) are measured to describe the bone resorption by osteoclast and to determine after how much time osteoclastic activity increases after the injection. • Mobility of patients will be assessed by the "Gross Motor Function Measurement score" and the 1 – minute walking test. Mobility in these patients is severely reduced due to immobility and fractures. We expect an increase of mobility comparing base line to week 48 by treating the children with denosumab. • Skeletal pain will be assessed by a visual pain scale every 3 months reflecting the effect of the therapy on chronic pain. • Additional to the evaluation of bone density at the spine changes of the whole body scan will be assessed at baseline and after 48 weeks in the routine measurements. This measurement allows a more generalized analysis of the skeletal situation compared to the assessment of the lumbar spine • Routinely x-rays of the lateral spine are taken once per year and will be used to describe the morphometry of the spine and the vertebrae. To quantify the changes the Severity Score of the spine will be used. • The muscle function will be assessed by using a ground reaction force plate on which the children will perform Balance test (standing as still as possible, or performing a chair rising test depending on their motor functions) • Additionally safety assessment was done by phone call every other week by the study nurse interviewing regarding AE and side effects. The rate and kind of the AE was documented on the CRF and assessed by an investigator regarding their importance for the safety of the trial participants.
Studiendesign	This pilot study is a phase II, open-label, single-arm, pilot study, evaluating the efficacy of treatment with denosumab in patients with OI, measured by the bone mineral density after 48 weeks after 36 weeks of treatment, the reduction of osteoclastic activity, as well as safety aspects of treatment with denosumab every

	12 weeks. DPD after denosumab injection at day 1, 2, 4, 8, 14, 21, 28, 42, 56, 70 Calcium levels after denosumab injection at day: 1, 2, 3, 4, 8, 14, 28, 56 Telephone interviews week: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46.

Study Design



Prüfmedikation / Behand-lungsstrategie	Trade name:	Prolia®
	INN (International Nonproprietary Name):	Denosumab
	Presentation:	Prolia 60 mg solution in syringe
	Dose:	1mg/kg body weight
	Manufacturer:	Amgen Europe B.V. Minervum 706 NL-4817 ZK Breda Niederlands
	Approved for:	Postmenopausal osteoporosis

<table>
<tr><td></td><td>Contraindications: Hypocalcemia</td></tr>
<tr><td>Behandlung/Intervention</td><td>Denosumab was given at the dose of 1 mg/kg body weight in 3-monthly intervals subcutaneously. This dosage was adapted from the adult dose recommendation. The intervals were chosen according to the intervals used in adults. This scheme is based on the half time of Denosumab. It has been reported that the antibody Denosumab is catabolized completely after 4-5 months. In an individual therapeutic approach four children with OI VI have been treated before the trial with a dose of 1mg/kg body weight according to the regime in adults with osteoporosis. DPD increased after 8-11 weeks. Therefore we applied the following dose after 3 months.
<table>
<tr><td>Study Week</td><td>Dosage</td></tr>
<tr><td>Week 0</td><td>1mg/kg body weight s.c.</td></tr>
<tr><td>Week 12</td><td>1mg/kg body weight s.c.</td></tr>
<tr><td>Week 24</td><td>1mg/kg body weight s.c.</td></tr>
<tr><td>Week 36</td><td>1mg/kg body weight s.c.</td></tr>
</table></td></tr>
<tr><td>Vergleichsbedingung/-medikation</td><td>Not applicable</td></tr>
<tr><td>Gesamtzahl Patienten</td><td>Calculated sample size prior to the trial: n = 10
Number of patients screened: n = 11
Number of patients included: n = 10
Drop outs: n = 0</td></tr>
<tr><td>Studienpopulation</td><td>The study population consists of 10 children (male: 7, female 3, median age 7.0 years). One subject failed screening. All 10 included patients completed the study. No further significant protocol modifications were seen.</td></tr>
<tr><td>Einschlusskriterien</td><td>•Documentation of diagnosis of OI by a known mutation in the causative gene (COL1A1 or COL1A2)</td></tr>
</table>

	•Male or female subjects between 5 years and 10 years of age. •Subjects must be treated at least 2 years with Neridronate prior to study entry. •Subjects receiving Neridronate before the study must be willing to discontinue therapy for a washout phase at least 3 months. •Written informed consent from legally acceptable representatives and from the patients, depending on their age.
Ausschlusskriterien	•Permanent hypocalcemia (<1.03 mmol/l ionized Calcium). •Subjects with reduced renal function (estimated GFR (Schwartz formula) <30ml/min/1.73m2). •Any other abnormal finding such as physical examination or laboratory evaluation, in the opinion of the investigator/ subinvestigator, is indicative of a disease that would compromise the safety of treatment with denosumab s.c. •Subjects participating in other clinical trials with investigational products 4 weeks prior to trial entry, during the trial and 4 weeks after the trial. •Subjects treated with other osteoanabolic or antiresorptive drugs. •Subjects who are unable to collect DPD urine samples or follow other study procedures. •Subjects with any kind of dependency on the investigator/ subinvestigator or employed by the sponsor or investigator/ subinvestigator •Subjects confined to an institution. •Contraindications in Information Sheet for Health Professionals (Fachinformation Prolia® in its currently valid version in Germany) •Diseases or findings that may have a significant effect on the target variables and which may therefore mask or inhibit the

	therapeutic effect under investigation
Darstellung der Demographie und Baseline-Charakteristika	11 children were screened for participation. One patient was excluded before the first denosumab application based on deterioration of general clinical and psychological condition. Ten participants completed the 48 weeks course of trial participation. A synopsis of baseline characteristics is given in table 1. Mean Height (± SD) increased from 105·0 cm (± 20·2) to 108·9 cm (± 21·2); p= 0·002; (Z-scores increased from -4·64 ± 3·71 to -4·62 ± 3·58; p=0·6953) during study participation. All patients received denosumab four times as planned. The injected dosage was in the mean 0·99; 1·0; 1·0; 1·01 mg/kg body weight at baseline, week 12, week 24, week 36, respectively [range 0·96 -1·05 mg/kg body weight].
Darstellung Wirksamkeit	**Primary objective:** ***Bone mineral density lumbar spine:*** All ten patients were included in the intention-to-treat analysis. Absolute aBMD increased from 0·507± 0·187 g/cm^2 to 0·612±0·229 g/cm^2 (mean±SD; p=<0·001) between baseline and week 48 (Table 2). Z-scores increased from -2·23±2·03 (mean±SD) to -1·27±2·37 (p=0·0006). Mean relative change of lumbar aBMD was + 19 % (95%-CI: 7-31%). Figure 1A presents individual aBMD data at baseline and week 48 plotted against age of patients. ***Secondary objectives:*** ***Changes of Bone metabolism markers:*** DPD levels decreased within four-eight days after each application in all patients. Calcium levels decreased parallel after each application in all children. DPD and Calcium levels are depicted exemplarily after the first application of all ten patients in Figure 2A/B. Over the entire treatment period, a downward drift of Osteocalcin and parathyroid hormone levels was detectable, whereas NTX and serum Calcium levels showed a tendency to

	rise. Mean levels are shown for visit 1-6 in figure 2C/D/E/F. Vitamin D levels were analysed at every visit: In 14 out of 60 analyses a vitamin D deficiency with a level between 10 and 20 µg/l was observed, in one analysis a severe deficiency with a level < 10 µg/l (8·2 µg/l at start) was detected. A secondary hyperparathyroidism was not observed at start or within the trial period. ***Bone mineral density total body less head:*** Absolute aBMD of the total body less head increased in the mean from 0·502 ±0·109 g/cm^2 to 0·551 ±0·144 g/cm^2 (p=0·052) (mean±SD) and age adjusted Z-scores from -1·96 ±1·521 to -1·39 ±1·66 (p=0·0036) between baseline and week 48 (Table 2). Additionally, BMC increased significant (p=0·0035) (Table 2). **Spine Morphometry**: Radiologic examinations of the spine revealed no new vertebral compression fractures. Evaluation of morphometry indices of the spine (L2/3/4) did not reveal significant changes (anterior-posterior index p= 0·3032; concavity index p= 0·9205). Changes of the anterior-posterior index and concavity index for L2, L3 and L4 are shown in table 2. **Mobility:** Mobility improved in the trial cohort. One participant suffered a traumatic femur fracture before end of trial and therefore was not tested at week 48. Results of the various mobility assessment tools are presented in Table 2. Individual changes in mobility between baseline and week 24/48 are presented graphically in figure 3 A/B. A mean increase of motor function 2·95% (GMFM-88 score 77·58±31·64% to 80·30±31·06 %; p=0·156) between baseline and week 48 was seen. Two patients presented with a full score (100 percent) at start, thus no improvement was possible. A relative change of one-minute walking distance of 18·47 % (absolute change from 86·6 m±26·83 to 97·6±18·0 m; n= 7; p=0·141) was detected. Six-minute walking distance could be

	evaluated in 6 patients. An increase from 486·5 m ± 166·5 to 530·2 m ± 164·5; p=0·058 (mean change of 11·82%) could be seen.
Darstellung der Sicherheit	Subcutaneous application of denosumab was well tolerated. Children reported local pain while receiving the injections. There were no discontinuations of trial medication application due to adverse events. Two serious adverse events were reported based on planned hospitalization (elective rod surgery after two traumatic fractures of the femur; slipping next to the swimming pool; tipping with the wheelchair). In summary, 75 adverse events were reported. 60 of these were declared as not related to denosumab representing common childhood illnesses. The 15 events assessed as possible related were: slight hypocalcaemia and general arthralgia. 60 adverse events revealed a CTC grade 1, 14 a CTC-Grade 2, and one a CTC-Grade 3 (flue with fever > 38·5°C). Two patients reported generalized joint pain after the second, third and last application of denosumab. Pain resolved within 14 days and was controlled by oral analgetic therapy. This side effect was declared as possible and probable related to denosumab treatment. In one child a mild hypocalcemia was reported a few days after denosumab application. This was declared as a certainly associated side effect. The observed side effects possibly related to denosumab were those cited in the investigators brochure. Four patients suffered a fracture within the study (tibia after traumatic injury, femur in two subjects after traumatic injury, clavicula after a mild trauma).
Statistische Methoden	All analyses were conducted using the full intention-to-treat set including all enrolled patients. Individual and mean changes over time in the various outcome variables were displayed graphically. The mean (absolute and relative) change in lumbar bone mineral density at 48 weeks and the mean change in BMD z-score were calculated with a 95% confidence interval and tested for significance using the paired t-test. Analogous methods were employed for secondary outcome variables as appro-

	priate. Cumulative lists of adverse events (AEs) and serious adverse events (SAE´s) were presented descriptively. P-values <0·05 were considered significant. Statistical analyses were conducted using SAS version 9.4.

ZUSAMMENFASSUNG:

We examined 10 patients (7 males) with genetically confirmed OI. Denosumab was administered subcutaneously with 1 mg/kg/body weight every 12 weeks. At baseline and 48 weeks, areal bone mineral density, safety and mobility aspects were evaluated.

ERGEBNISSE WIRKSAMKEIT:

All ten patients were included in the intention-to-treat analysis. Absolute aBMD increased from 0·507± 0·187 g/cm^2 to 0·612±0·229 g/cm^2 (mean±SD; p=<0·001) between baseline and week 48 (Table 2). Z-scores increased from -2·23±2·03 (mean±SD) to -1·27±2·37 (p=0·0006). Mean relative change of lumbar aBMD was + 19 % (95%-CI: 7-31%). Figure 1A presents individual aBMD data at baseline and week 48 plotted against age of patients. Individual and mean age- adjusted Z-scores for aBMD are shown in Figure 1B.

ERGEBNISSE SICHERHEIT:

In summary the toxicity seen in this trial is consistent with the side effects given in the reference document. No further risks were observed during this trial. Overall the trial medication has been well tolerated. There were no deaths and no dropouts related to the trial medication or related to adverse events. Two serious adverse event were considered to be unrelated to the trial medication. At the present stage the potential benefit of the trial medication seems to overweigh the risks.

SCHLUSSFOLGERUNG:

In summary, this first prospective clinical trial of denosumab application in OI children gives evidence

1.that denosumab has a high efficacy to increase areal bone mineral density at the lumbar spine and to avoid new vertebral compression fractures,

2. that children under denosumab treatment show an increase of their height

3. that children with OI treated with denosumab could maintain their mobility levels,

4. that denosumab supresses bone resorption in children over 10-12 weeks,

5. that denosumab seems to be safe in a one-year treatment course if a sufficient calcium and vitamin D substitution is provided.

Although we were able to prove treatment efficacy and safety of denosumab in the short time,

further studies in larger (multicenter) settings are clearly needed to better clarify the mechanism of action, the influence on height development and the long term outcome under therapy. At the very end, individualized translational therapeutic concepts for patients with an orphan disease like OI, should be aimed.

Table 1. Baseline characteristics of the study population at trial entry

Participants n	10
Male n (%)	7 (70)
Age Mean [years] (range)	7·00 (5·02 – 10·96)
Height Mean [cm] (range) Z-Scores ± SD	105·0 (66·0 – 134·0) -4·64 ± 3·72
Weight Mean [kg] (range)	19·27 (7·8 – 27·3)
BMI Mean [kg/m^2] (SEM)	17·6 (13·1 – 33·0)
OI Type 1/4 n (%) Able to walk (GMFM item 69) n (%)	8 (80) 7 (70)
OI Type 3 n (%) Able to walk (GMFM item 69) n (%)	2 (20) 0 (0)
Causative gene *COL1A1* n (%) *COL1A2* n (%)	 7 (70) 3 (30)

Table 2. Changes of areal bone mineral density, morphometry, mobility, and height between baseline week 24, and week 48 of the trial

(mean ± SD)	Number of patients	Baseline	Week 24	Week 48	Change baseline – week 48 [95% CI]	p-value
BMD lumbar vertebrae L2-L4 (g/cm²)	10	0·5070± 0·1868	No DXA and x-ray assessment based on radiation guidelines	0·6118± 0·2294	+ 0·10 [0·06; 0·15]	< 0·001
BMD lumbar vertebrae L2-L4 Z-score	10	-2·230± 2·0281		-1·270± 2·366	+ 0·96 [0·597-1·323]	0·0006
BMD total body without head (g/cm²)	9	0·5019±0·1087		0·551±0·144	0·049 g/cm² [-0·0005-0·099]	0·052
BMD total body without head Z-score	9	-1·9555±1·522		-1·388±1·658	0·566 [0·30738-0·8259]	0·0036
BMC total body without head (g)	10	364·170±213·246		448·810±274·252	85 g [36-134]	0·0035
Morphometry Spine Anterior-posterior index (1-ah/ph)*100	8	-16·18±41·46		-4·475±14·67	-	0·3032
Morphometry Spine Concavity index (1-mh/ah)*100	8	5·436±25·7		7·322±23·96	-	0·9205
GMFM 88 (%)	9	77·58± 31·64	79·69± 31·33	80·3± 31·06	2·722 [-0·8253-6·27]	0·1563
Walking 1 Min	7	86·57± 26·83	93·0± 15·28	97·57± 18	11 [-3·633-	0·1406

(m)					25·63]	
Walking 6 Min (m)	6	486·5 ± 166·5	530·2 ±164·5	535·2 ±159·8	48·7 [18·561-78·773]	0·058
Height Mean [cm] (SD)	10	105·0 (± 20·2)	-	108·9 (± 21·2)	3·9 [2·98-4·82]	0·002
Height Mean Z-Scores ± SD	10	-4·64 ± 3·72	-	-4·62 ± 3·58	0·024 [-0.3-0·3483	0·6953

Figure 1A/B: Individual changes of lumbar spine vertebrae 2-4 areal bone mineral density and Z-scores between baseline (week 0) and week 48

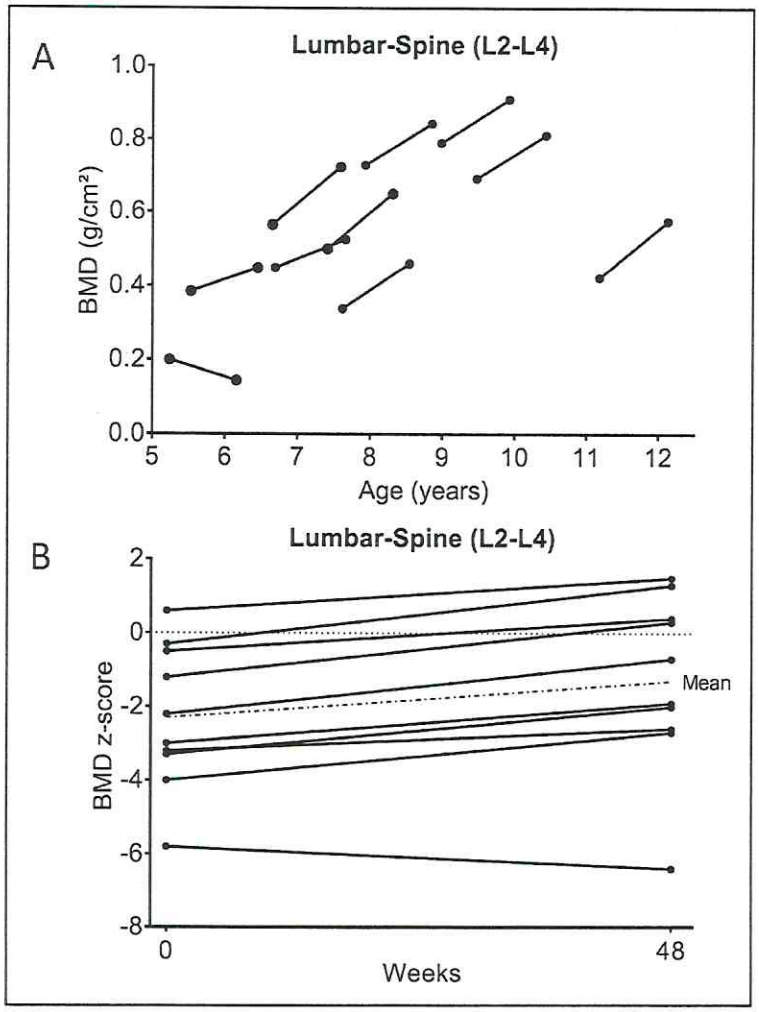


Figure 1A presents the individual absolute lumbar spine areal bone mineral density values (L2-L4) plotted against age at trial entry (baseline) and week 48. In Figure 1B age-adjusted Z-scores and their change are shown individually and as mean for 10 patients between baseline and week 48.

Figure 2 A-F: Courses of bone metabolism markers within the trial

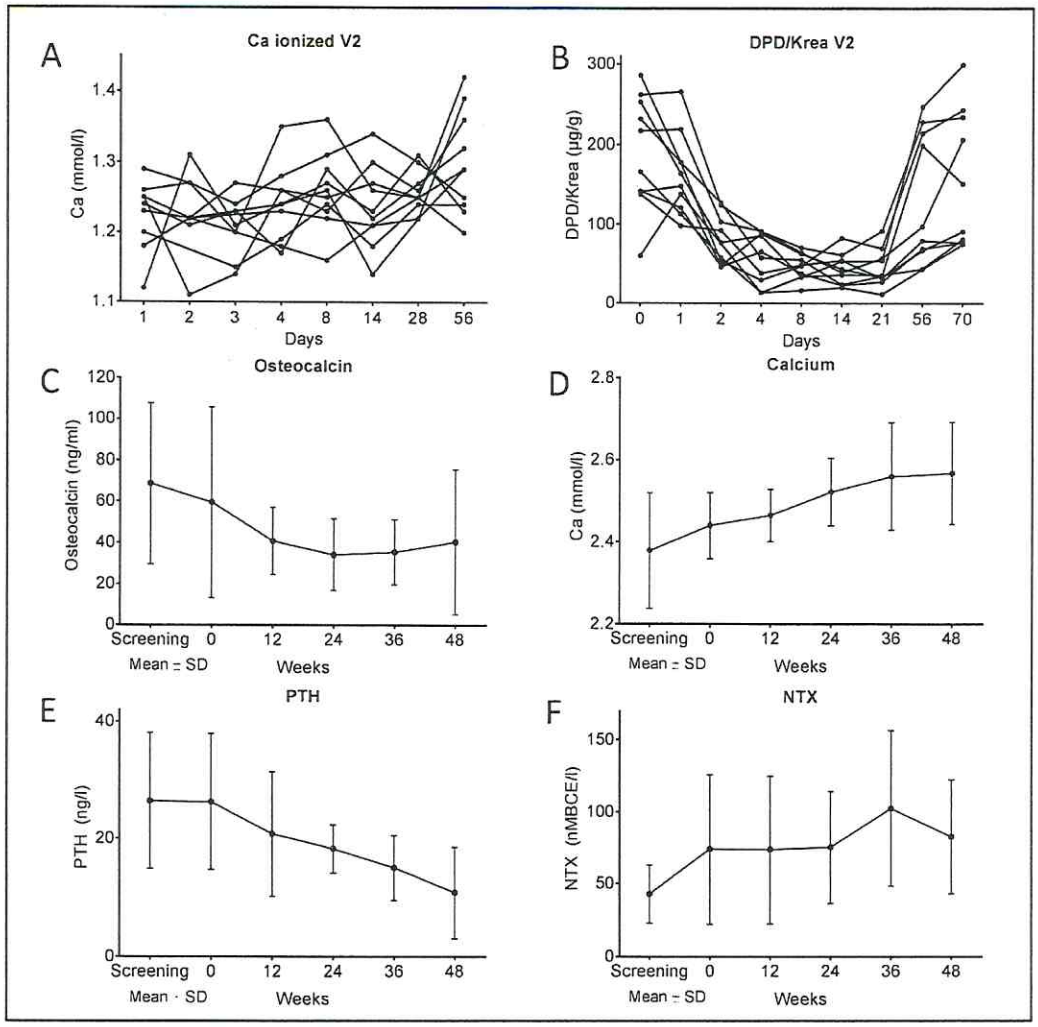


Figure 2A/B presents exemplarily the individual courses in ten patients of ionized serum calcium (Ca ionized) and urinary desoxypyridinoline/creatinine (DPD/Krea) levels after the first application of denosumab at trial week 0. Presented are all blood and spot urine controls from the day of application (day 0) to day 70 post first denosumab injection (one trial interval of 12 weeks). The next dosage was given at day 84 (not shown here). In figure 2C-F mean levels +/- SD of the bone metabolism markers Osteocalcin (C) , total serum calcium (D), parathyroid hormone (PTH), and serum N-Telopeptides (NTX) at the different visits (Screening, baseline, week 12, week 24, week 36, and week 48; whole trial intervals!) are demonstrated.

Figure 3: Individual changes of Motor Function (GMFM-88, One-minute walking distance) between baseline, week 24, and study week 48

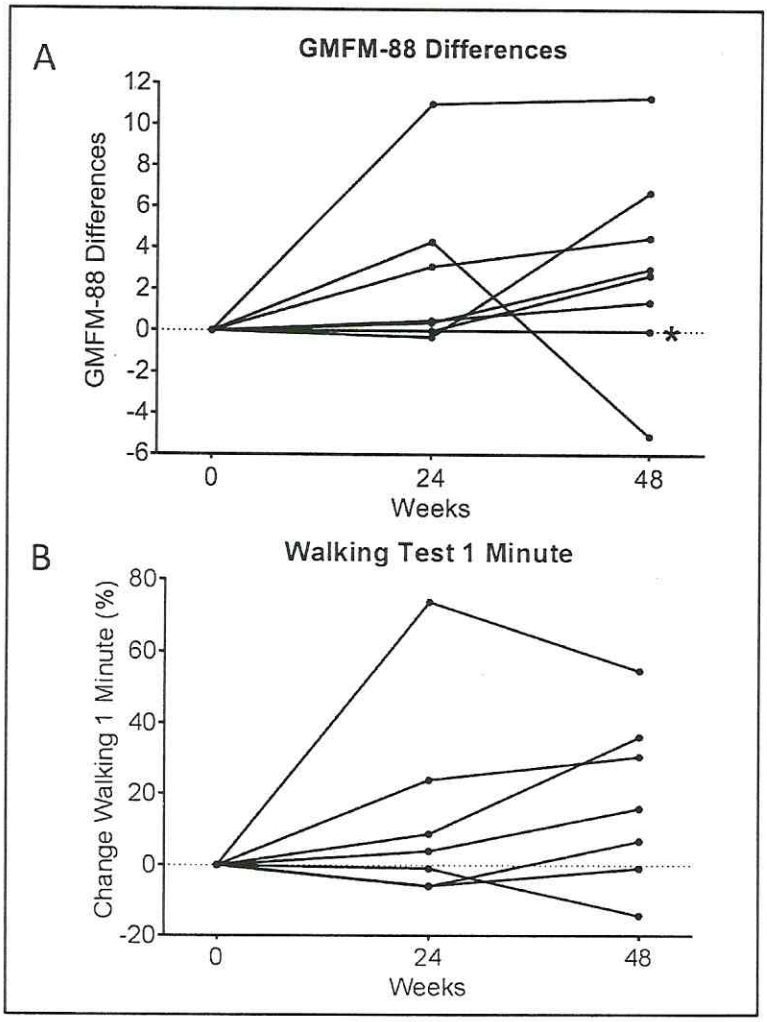


Figure 3A shows the individual absolute differences of 9 study participants in the GMFM-88 assessments at baseline, week 24, and 48. 2 children started with a maximum of 100 % in the GMFM-88 and maintained their mobility levels until week 48. Therefore no changes are detectable in these 2 children (marked by the asterisk) lying on the dotted line which marks the line of no difference. In figure 3B the individual percent changes of walking distance are presented between week 0, week 24, and week 48 in the 7 children who were able to walk at trial entry.