Synopsis

Name of Sponsor	Evangelisches Krankenhaus Lutherhaus gemeinnützige GmbH Hellweg 100 45276 Essen
Name of Finished Product	Fosamax®
Nam of Active Substance	Alendronate Sodium
Title of Study	Comparison of the effect of an ongoing treatment with alendronate or a drug holiday on the fracture risk in osteoporotic patients with bisphosphonate long term therapy (BILANZ)
Investigators	[redacted] (coordinating investigator), et al. A listing of all investigators is provided in Appendix.
Study centre(s)	57 study centres in Germany
Publication	None as of date of report
Studied period: Date of first enrolement Date of last completed	First patient enrolled: 28 February 2012 Number of participants who completed the planned two year study period: None The study was early terminated on March 08 2013 due to a low recruitment rate.
Phase of development	Clinical phase IV in women, phase III in men
Objectives	The primary objective of the study was to examine whether a continued treatment with alendronate for another two years in osteoporotic patients with a high fracture risk and a preceding therapy with bisphosphonates for at least four years is superior in reducing the incidence of new osteoporotic fractures compared to placebo. Secondary objectives were mortality and a composite endpoint of fractures and mortality
Methodology (Study design)	Prospective, 24-month, multicentre, randomized, placebo-controlled, double blind
Number of patients (planned and analysed)	Planned: 7000 Analysed: 436
Diagnosis and main criteria for inclusion	Diagnosis: Osteoporosis (DXA-T-Score < -2,0 at lumbar spine, total hip or femoral neck), high fracture risk Inclusion criteria:

	- Postmenopausal women, men > 60 years, - DXA T-Score at lumbar spine, total hip or femur neck < -2,0 before the start of the bisphosphonate therapy or at baseline, or at least one low trauma vertebral fracture grade 2-3, or multiple low trauma vertebral fractures independent of bone mineral density - Pretreatment with bisphosphonates for at least four years - 10 year risk for hip fractures and radiological vertebral fractures ≥ 30% according to the DVO-Guideline on Osteoporosis 2009
Test product, dose and mode of administration, batch number	Alendronate Sodium, 70 mg administered orally once weekly Manufacturer: Merck & Co. Inc, USA, batch numbers [redacted]
Duration of treatment	Planned: 24 months Median duration: 6.2 months (minimum 0, maximum 10.7 months) The study was early terminated due to a low recruitment rate.
Reference therapy, dose and mode of administration, batch number	Placebo, administered orally once weekly Manufacturer: Merck & Co. Inc., USA, batch numbers [redacted]
Criteria of evaluation: Efficacy, Safety	Efficacy: Incidence of new osteoporotic low trauma fractures, except for fractures of fingers, toes and skull; mortality; and combined incidence of osteoporotic fractures and mortality Safety: Serious adverse events, death
Statistical methods	The intention-to-treat population (ITT) consisted of all randomized patients. The primary objective was to show the superiority of alendronate therapy compared to placebo in reducing the incidence of osteoporotic fractures. Determination of differences between the two treatment arms regarding osteoporotic fractures in the course of two years was planned by logistic regression, adjusted for number of pre-existing vertebral fractures and study centre. Report of the p-values was planned based on a likelihood ratio test. The sample size calculated to detect a difference in incident fractures between placebo and alendronate with a power of 90% and an alpha of 2.5% based on assumptions on incident fractures in the population, drop-outs, and pretreatment effects with bisphosphonates on fractures incidence, was 3500 for each treatment arm.
Summary of Efficacy results	Forty one study sites were actively recruiting patients. The recruitment rate was considerably lower than expected. In total, 436 eligible subjects were randomised (215 on alendronate, 221 on placebo). 51 of the randomized subjects dropped out before receiving study medication. The remaining 385 patients received at least one dose of study medication (188 alendronate, 197 placebo). Forty three patients dropped out of the study after receiving study medication. Two deaths occurred during the study period. At the time of the early

	termination of the study there were 342 active study participants. The following analysis includes all 436 randomized patients. Mean duration of bisphosphonate treatment prior to study inclusion was 5.8 years. 397 (91.1%) of the study population were women. The mean age was 74.8 ±7.0 (SD) years. 24.3% of the patients who took part in the study were 80 years of age or older. Placebo treated patients were slightly older (mean age 75.3±6.9 years) compared to alendronate treated patients (mean age 74.3±7.1) years). Placebo treated patients had a lower average quality of life as assessed by the EQ-5D index at the beginning of the study (placebo 0.69±0.22, alendronate 0.73±0.17), a higher average number of reported comorbidities (placebo 4.0 ±2.1, alendronate 3.6±2.1) and a higher average number of reported clinical fracture risks (placebo 1.9±1.3, alendronate 1.8±1.3), as compared to alendronate treated patients, respectively.The percentage of patients with prevalent radiological vertebral fractures prior to study inclusion was also higher in the placebo group (52.5%) as compared to the alendronate group (42.3%). 5 osteoporotic incident clinical fractures occurred during the study period in the alendronate group and 5 in the placebo group, respectively. 2 patients in the placebo group died during the study period and none in the alendronate group. The combined number of osteoporotic fractures and death in the alendronate group was 5 accordingly, as compared to 7 in the placebo group. 4 fractures unrelated to osteoporosis occurred in the alendronate group and none in the placebo group. Due to the low number of fractures, no conclusive efficacy results can be reported.
Safety results	The study treatment was safe and well tolerated and no new or unexpected safety signals were observed. The following analysis includes all 385 randomized patients who received at least one dose of study medication (alendronate 188, placebo 197). The overall proportion of patients reporting at least one adverse event (AEs) was 50% in the alendronate group and 57.4% in the placebo group. The most frequent AEs were joint pain (26.2%), muscle pain (17.1%), and dizziness (15.6%), respectively. Serious AEs (SAEs) of all randomized participants who had received at least one dose of study medication were reported by 16.5% of the patients in the alendronate group and 19.3% of the patients in the placebo group. The most frequent SAES were injuries and surgical procedures. One case of osteonecrosis of the jaw was observed in an alendronate treated patient. One case of an atypical femur fracture occurred in a placebo treated patient.

	Two subjects in the placebo group died before termination of the study. A third subject in the alendronate group died shortly after study termination for reasons that were not drug-related. The proportion of patients with SAEs who received at least one dose of study medications and dropped out of the study was 3.2% in the alendonate group and 4.1% in the placebo group with no relevant differences between the two treatment groups.
Conclusion	Due to a low recruitment rate, the study had to be early terminated. The small number of analysed patients does not allow any new conclusion concerning the efficacy of a continuous treatment with alendronate versus a drug holiday with regard to incident fractures in patients on long-term treatment of osteoporosis. No new unexpected safety signals were observed.
Date of report	26. February 2014

Appendix