Exploratory Six Month Phase IIa Study of a Potential Disease Modifying Drug in Patients with OA of the Knee

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BACKGROUND

Osteoarthritis (OA) is the most common form of arthritis worldwide with rising incidence and prevalence in part due to ageing and obesity. In Western populations it is one of the most frequent causes of pain, loss of function, and disability in adults. In the US, Osteoarthritis affects 30% of the population with nearly 1 in 2 people expected to develop knee osteoarthritis by age 85. Over 40,000 total knee and hip replacement procedures were performed in 2013, the majority for OA, each costing between $15,000– $31,900.

Despite its large disease burden, there are currently no approved disease-modifying drugs available which modify structural progression of OA. Conventional treatment of OA is mostly symptomatic and costly. Therefore, there is urgent need for a disease modifying osteoarthritis drug (DMOAD).

Bisphosphonates have been evaluated as DMOAD. Zoledronic Acid (ZA) is the most potent bisphosphonate and is approved for prevention and treatment of osteoporosis, Paget's disease and certain bone cancers. A phase 2 randomized controlled trial of ZA in OA of knee in Australia (ZAP study, Zoledronic Acid for Knee Pain) showed efficacy at six months of ZA in decreasing bone marrow lesions in OA by MRI.

This study describes the ability of a new formulation of ZA, VOLT01 (US patent # 8,864,843), to treat OA. In comparison, to ZA, VOLT01 showed superior efficacy in controlling osteoarthritis pain.

MATERIAL AND METHODS

In a single blind, single center study, 32 subjects with knee osteoarthritis were randomized to receive either intravenous (IV) VOLT01 or ZA in a 1:1 ratio. Inclusion criteria included OA of knee per ACR criteria, and no subject was excluded based on severity of knee OA. They received a single intravenous infusion of either VOLT01 or ZA over a period of 30 minutes. They were followed at the end of 48 hours, 3 months and six months.

At the end of 48 hours, they were asked for complaints of fatigue, body aches, joint pains, fever and myalgia, symptoms that commonly accompany ZA infusions and are known as post dose syndrome (PDS).

At three months and six months, they were asked about knee pain using a simple 100 mm visual analogue scale (VAS) from baseline (mean values). Subjects were asked about the level of pain without taking rescue medications (NSAIDs or tramadol). Bone marrow density (BMD) was determined at baseline and six months to detect osteoporosis to confirm effect of ZA or VOLT01.

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STUDY RESULTS

VOLT01 vs ZA in Knee Osteoarthritis

Cohort	ZA	VOLT01
Δ Mean VAS at six months	-10mm	-35mm
PDS (reporting/total)	9/16	2/16
Worsening of BMD	0	0

Table 1. Results of the 32 patient study comparing VOLT01 to Zoledronic Acid in Knee Osteoarthritis. Change in VAS is reported as the mean for the cohort.

VOLT01 was statistically significantly superior to ZA in efficacy (measured by VAS) with $p<0.05$. Due to budgetary constraints, other measurements such as WOMAC, MRI, etc were not done. Statistical analysis was done by an independent contractor (Percept Pharma Services, NJ).

VOLT01 was also superior to ZA in safety (measured by PDS). There were no deaths in the study. There were no SAE is the VOLT01 cohort, one in the ZA cohort where the subject had chest pain and tightness. He was evaluated in the emergency room and found not have acute coronary disease. A skin test to ZA was negative.

CONCLUSION

OA is a major, but poorly understood, public health problem. It is anticipated that OA will become the fourth leading cause of disability by the year 2020 according to the World Health Organization. Current treatments include NSAIDs, steroids, and eventual joint replacement. There is currently no treatment that stops or delays progression OA.

In this study, VOLT01 clearly demonstrated superior efficacy in controlling knee OA pain when compared to ZA alone. In addition, the PDS normally associated with ZA administration, was greatly reduced in VOLT01. It is important to note the sustained effect of VOLT01 treatment. Patients in these cohorts were followed for 6 months, with a significant reduction in pain still being reported at the 6 month endpoint. This sustained effect suggests that disease is being modified, as was also suggested by the ZAP study. If true, VOLT01 will be the first Disease Modifying Osteoarthritis Drug (DMOAD), with the potential to become a first line treatment for OA.

Expanded studies are already underway, with a Phase III trial in knee OA in Australia. Levolta is also targeting a placebo-controlled phase III trial in Russia. These trials will expand on the data reported here. They will be 1-2 year multicenter studies with large patient cohorts. In addition to VAS, efficacy will be assessed by WOMAC and quality of life instruments such as AQoL. Disease modifying aspects of VOLT01 will be assessed using MRI and X-rays.

OA is a major burden on individuals, health care systems, and social service systems and this is expected to increase dramatically as our population ages. Successful VOLT01 Phase III trials will make it a first line defense against OA, providing payers with a pharmacoeconomic benefit through reduced joint replacement surgeries and significantly enhanced quality of life for patients.