



ORAZOL[®]

**Novel Approach to Adjuvant Therapy
For Improving Outcomes in Breast Cancer**

Q1 2011

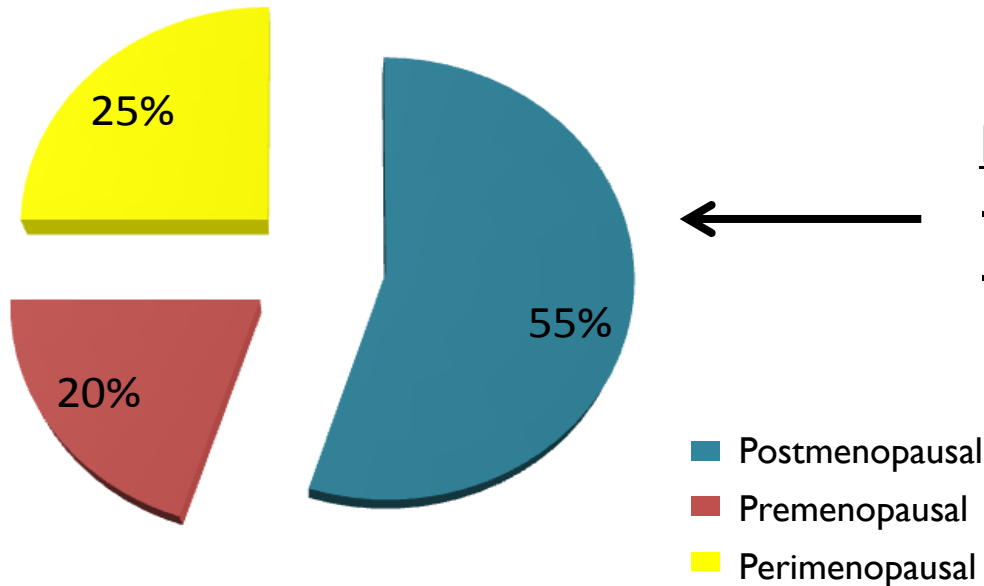
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Orazol – Oral Zoledronic Acid to Improve Outcomes in Breast Cancer

- ❑ **High potential product** – blockbuster market
 - ❑ Early stage breast cancer is a multibillion dollar market with limited new treatment options
 - ❑ Orazol has US patent protection to 2027
- ❑ **Multi-year treatment** to reduce risk of recurrence and death
 - ❑ 29% reduction ($p=0.017$) in the risk of death for postmenopausal women*
 - ❑ 21% reduction ($p<0.05$) in the risk recurrence or death for postmenopausal women*
- ❑ **Abbreviated development path**
 - ❑ Clinical development plans agreed with EMEA and FDA
 - ❑ Ready for Phase III development with pharma partner
- ❑ **Limited clinical risk**
 - ❑ Extensive data from large scale zoledronic acid studies in early stage breast cancer
 - ❑ Successful Phase II data with Orazol formulation

Orazol Opportunity - Postmenopausal Breast Cancer Population

Breast Cancer Population¹



Primary Target

- Postmenopausal population
- Adjuvant to existing treatment

Menopausal Status

- Menopausal status (pre or postmenopausal) is an important differentiating factor
- Premenopausal women have much higher levels of estrogen in circulation
- Orazol has demonstrated efficacy in the absence of estrogen

¹DataMonitor, Stakeholder Insight: Breast Cancer (Hormone Receptor-Negative) Triple-negative breast cancer, November 2010

Orazol Opportunity - Postmenopausal Breast Cancer Population

SEER CANCER DATABASE* (US)			
		MENOPAUSAL	
Breast Cancer	Population	POST	PRE
Annual incidence	201,728	110,950	90,777
5yr prevalence	802,387	441,313	361,074
10yr prevalence	1,467,816	807,299	660,517

* Estimated US Cancer Prevalence Counts on Jan 1 2007

Postmenopausal Breast Cancer Population

- ❑ **110,000 diagnoses of postmenopausal breast cancer annually in the US**
- ❑ **All patients eligible for long-term adjuvant treatment e.g. 5+ years**
- ❑ **A 5 year treatment period equates to 440,000 addressable patients**
- ❑ **Aromatase inhibitors currently sell \$1.6Bn in this market (\$3Bn worldwide)**

Zoledronic Acid – Clinical Trials

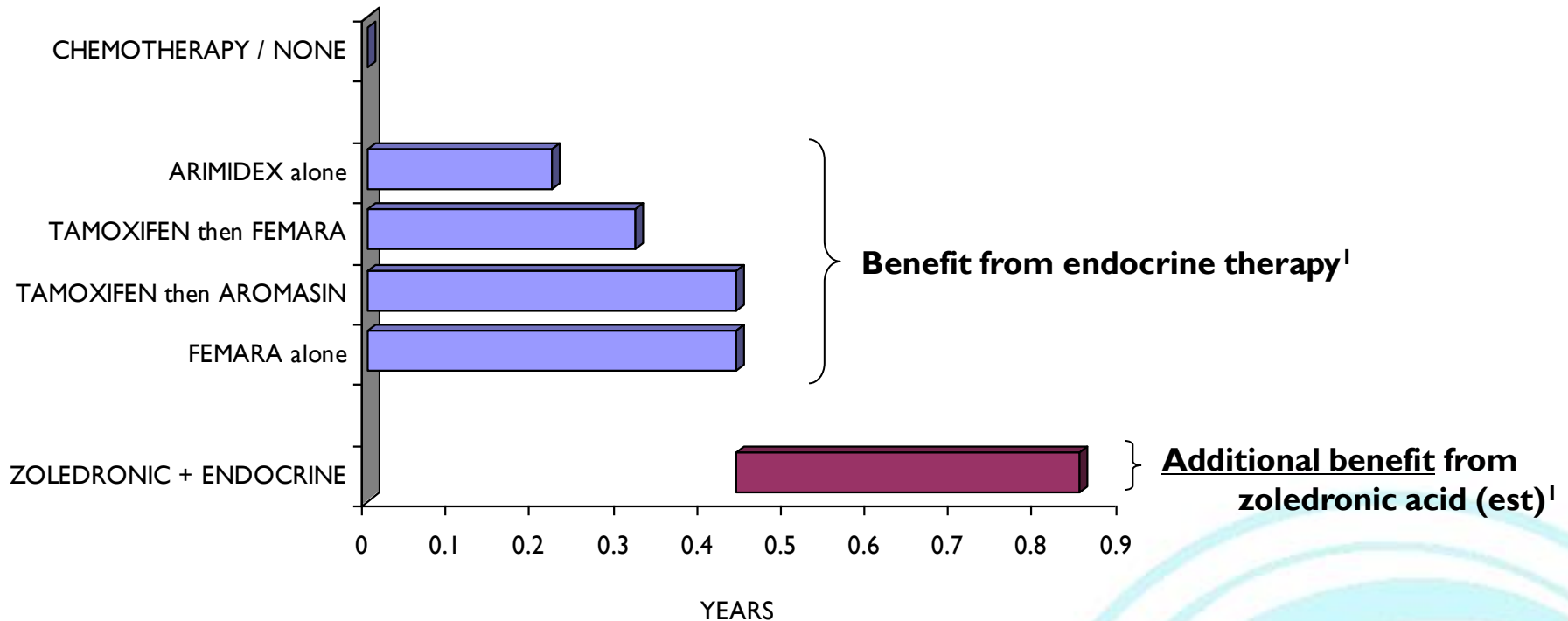
ZOLEDRONIC ACID ADJUVANT BREAST CANCER TRIALS

Trial	Drug	Size	Population	Estrogen	Results
AZURE (Coleman) POSTMENOPAUSAL	zoledronic acid	1,101	POSTMENOPAUSAL	ABSENT	29% reduction in the risk of death ($p=0.017$) 21% reduction in the risk of disease or death ($p<0.05$)
ABCSG-12 (Gnant)	zoledronic acid	1,803	PREMENOPAUSAL (with hormonal suppression)	ABSENT	36% reduction in the risk of disease progression ($p=0.01$) 35% reduction in the risk of disease recurrence ($p=0.02$)
Z-FAST / ZO-FAST	zoledronic acid	1,667	POSTMENOPAUSAL	ABSENT	52% reduction in the risk of disease or death ($p=0.0396$) 56% reduction in the risk of disease ($p=0.0401$)
AZURE (Coleman) PREMENOPAUSAL	zoledronic acid	2,258	PREMENOPAUSAL	PRESENT	No effect

- ❑ **Efficacy demonstrated in both postmenopausal and premenopausal patients where estrogen is absent**
- ❑ Zoledronic acid reduced cancer recurrence and disease progression in early and late stage breast cancer
- ❑ Reduction in cancer recurrence and disease progression at all key sites

Zoledronic Acid – Efficacy in Adjuvant Therapy

INCREASE IN OVERALL SURVIVAL



- **Endocrine therapy is estimated to prolong overall survival by 0.2 – 0.4 years¹**
- **Adding zoledronic acid to endocrine therapy is estimated to deliver an additional 0.4 years in overall survival¹**
- **Zoledronic acid has the potential to become ‘standard of care’**

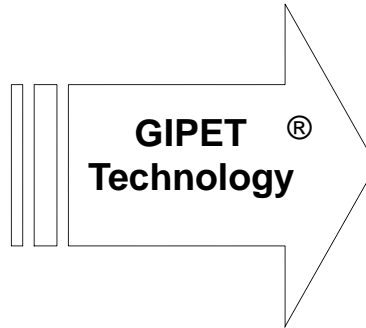
Breast Cancer – Adjuvant Therapy Options

CANCER SUB-TYPE DETERMINES ADJUVANT TREATMENT

CANCER SUB-TYPE	INCIDENCE	STANDARD OF CARE	PROGNOSIS
HORMONE POSITIVE	80%	ENDOCRINE THERAPY	MEDIUM - GOOD prognosis
HERCEPTIN POSITIVE	7%	HERCEPTIN	POOR prognosis
TRIPLE NEGATIVE	13%	CHEMOTHERAPY	POOR prognosis

- ⇒ **Orazol has shown a benefit in all cancer sub-types**
- ⇒ **This benefit is additive to existing ‘standard of care’ efficacy**

Orazol – Background

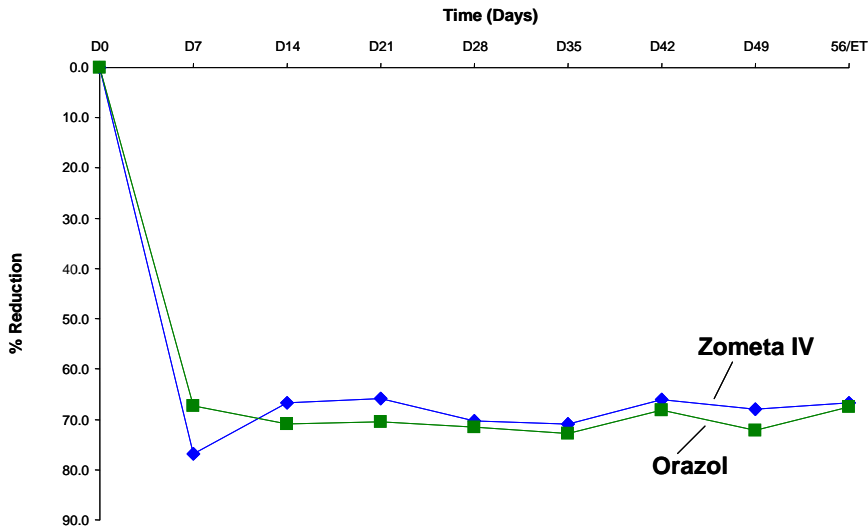


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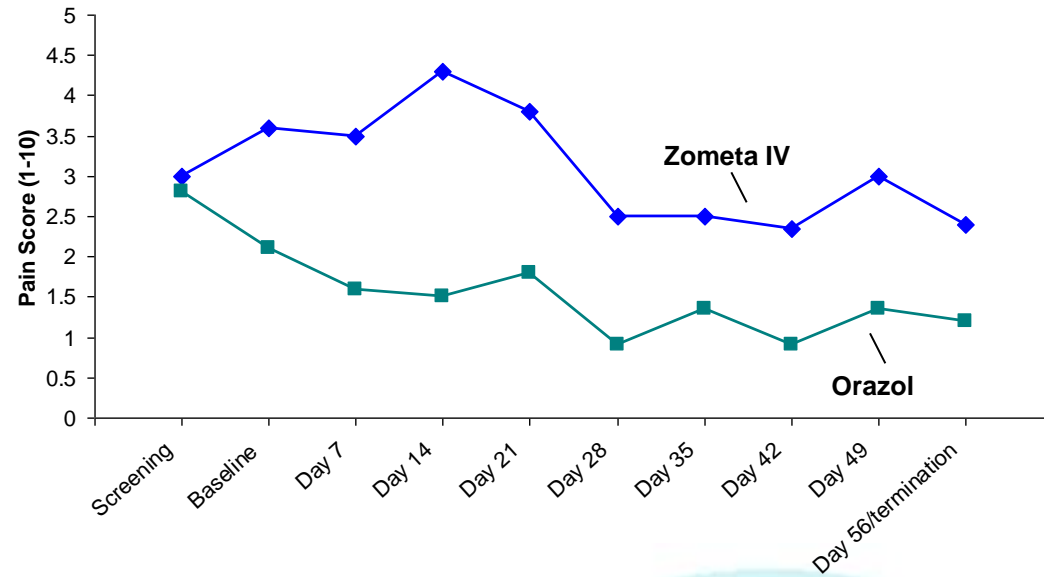
- ❑ Orazol was originally developed as an oral tablet of Zometa (zoledronic acid formulated as a monthly infusion)
- ❑ Zometa is indicated for the symptoms of bone metastases (pain, fractures, etc.) in late stage cancer patients
- ❑ Zometa (Novartis) had 2009 worldwide sales of \$1.5Bn

Orazol – Development

NTX, Urine % Reduction from Baseline



Brief Pain Inventory



Orazol Phase II data demonstrated:

- ❑ Similar delivery of zoledronic acid to the bone between the two dosage forms (4mg monthly infusion vs. 20mg weekly tablet)
- ❑ Similar efficacy as measured by standard bone turnover biomarkers (CTX, u-NTx)
- ❑ Improved efficacy for bone pain
- ❑ Improved safety and tolerability profile

Orazol – US Development Plan Status

- Agreement with FDA on Phase III study details
- Regulatory route: 505(b)(2) – SINGLE PHASE III STUDY
- Indication: adjuvant breast cancer therapy
- Primary endpoint: Disease Free Survival (DFS)
- Population: Postmenopausal Stage II and Stage III breast cancer patients at high risk of recurrence
- Patient numbers: 570 patients (based on hazard ratio derived from Gnant study)
- Recruitment: 18 months
- Treatment: 18 months
- Drug safety monitoring committee to allow adjustment of trial length to ensure sufficient number of study events

Next stage will be development of an SPA

Orazol – Limited Clinical Risks

- ❑ Orazol pivotal trial will be optimized based on previous successful studies with zoledronic acid infusion:
 1. Recruit postmenopausal women - estrogen is ABSENT
 2. Oral formulation allows higher dosing increasing potential efficacy
 3. Enrichment of patient population at high risk of breast cancer recurrence will be conducted to expedite collection of study events and shorten trial length
 4. An interim analysis will allow trial length to be adjusted to ensure required number of events is reached
 5. DFS (Disease Free Survival) will be the primary endpoint
- ❑ Only one single pivotal trial is necessary for approval

EU Development Pathway:

- Phase III protocol agreed with CHMP (Europe)
- Regulatory route: hybrid abridged application
- Indication: prevention of skeletal related events (bone metastases effects) in advanced malignancies
- Endpoint : u-NTx (i.e. Biomarker for bone turnover)
- Population: prostate and breast cancer patients with identified bone metastases
- Number: 420 patients
- Treatment : 6 months treatment, 6 months follow-up

Orazol – Development Strategy

1. Obtain approval for bone metastases indication in the EU
2. Obtain approval for adjuvant therapy indication in the US
3. Leverage US adjuvant data to obtain adjuvant therapy indication in the EU & ROW

Orazol – Patent Information

- ❑ **Base GIPET Patent - P24,375**
 - ❑ Issued US (09/510,560) with claims directed to bisphosphonates
 - ❑ Issued in EU (00905186.3) and allowable in CA (2363123) with broad claims
 - ❑ Continuation allowable in US (12/172,707) with claims directed towards ZA
 - ❑ Continuation in progress in US (12/553,196) on base patent
 - ❑ Expiry 22 Feb 2020

- ❑ **Specific product patent P31,578 on Orazol**
 - ❑ Issued in US (7,704,977)
 - ❑ Filed WW (EP 07755266.9)
 - ❑ Claims directed to tablet strengths and % bioavailability
 - ❑ Expiry 9 Apr 2027

- ❑ **Further patent filings with expiry in 2030/31**

- ❑ **Independent review of Orazol patent portfolio**
 - ❑ Engaged US patent litigator with expertise in acting for generic companies

Orazol - A High Potential Late Stage Licensing Opportunity:

- ❑ Fast route to market based on existing indication in breast and prostate cancers supportive care in EU (same label as Zometa)

- ❑ New indication in breast cancer adjuvant therapy in US
 - ❑ Demonstrated clinical efficacy
 - ❑ Large patient population
 - ❑ Chronic therapy (up to 5 years)
 - ❑ No generic competition
 - ❑ Priced as a new therapy

- ❑ Potential to extend new indication to EU and ROW

- ❑ Potential use in other oncology indications including orphan indications