Introduction

• Cevira® (hexaminolevulinate) is a key late stage asset for treatment of pre-cancerous lesions and HPV

• Human Papilloma Virus (HPV) is a highly prevalent sexually transmitted disease impacting women of child-bearing age

• High unmet medical need for non-invasive, safe treatment options

• Cevira removes HPV and CIN selectively, preserving underlying normal tissue and the cervix remains competent

• Successful Phase 2b results of Cevira at 5% optimal dose demonstrated
  - significant and sustained efficacy in CIN 2 patients after 6 months
  - sustained clearance of HPV 16/18, the high risk subtypes, after 6 months

• Results are significant and lay the foundation for the Phase 3 registration program, to be undertaken with a global development and commercialization partner

1) Selectively Fluorescing HPV-infected precancerous tissue

Photo courtesy of Dr. Hillemanns, Hannover
Breakthrough Platform Technology Designed for Ease of Use

- First fully integrated drug-delivery device in photodynamic technology

- Novel single use, disposable intra-vaginal device developed for ease of use
  - Obviates clinical and commercial barriers

- Simple application in office setting
  - Does not require additional equipment
  - Auto-activation
  - Patient free to resume normal daily activities

- Designed to treat the entire epithelial sheet

- Outstanding Physician and Patient Acceptance
Program

- HPV Related Diseases of the Cervix
  The Need for Novel Therapies
  - Ole Erik Iversen, MD, PhD
    Department of Obstetrics and Gynecology
    Haukeland University Hospital, Bergen, Norway

- Results of Phase 2b Clinical Trial
  - Peter Hillemanns, MD, PhD
    Principal Investigator
    Department of Gynecology and Obstetrics
    University Hospital, Hannover, Germany

- Conclusion and Q&A
  - Kjetil Hestdal, MD, PhD
    President & CEO
HPV Related Diseases of the Cervix
The Need for Novel Therapies

Ole Erik Iversen, MD, PhD
Department of Obstetrics and Gynecology
Haukeland University Hospital
Bergen, Norway
Human Papilloma Virus

- Human Papilloma Virus (HPV) is a highly prevalent sexually transmitted disease
- Affects 80% women of all women during their lifetime
  - 300 million woman infected worldwide
  - 11.4% prevalence in the general population
  - Highest incidence in ages 18-35 years
- Well established cause of Cervical Intraepithelial Neoplasia (CIN) and cervical cancer
- Highly oncogenic subtypes 16 and 18 causal factor in
  - ~70% all cervical cancers
  - ~50% all high grade lesions
  - ~25% all low grade lesions

References: WHO, 2010
Progression of HPV to CIN and Cervical Cancer

- Although majority of HPV infections will spontaneously regress, ~10-20% progress to precancerous lesions (CIN) within 2 years

- CIN
  - Close association between HPV induced cell changes and invasive cancer
  - Disease within its own right, CIN 2+ requires treatment
  - 30 million women globally with low grade lesions/CIN 1
  - 10 million women globally with high grade lesions/CIN 2

- Cervical cancer
  - 2nd most frequent cancer in females worldwide
  - ~530,000 new cases diagnosed annually
  - ~280,000 deaths

Current Screening Programs are Insufficient

- PAP testing (cytology), although considered gold standard for screening, misses 30-50% of cancers
  - Sensitivity of a single PAP test ~50%
- Current consensus guidelines in US recommend primary HPV Co-testing only in patients ≥ 30 years of age
  - Recent data supportive of HPV testing without cytology as sufficient screening tool
- Adherence to recommended screening and surveillance variable across geographies, even in developed countries
  - 30-75% of patients adhere to protocol
- Colposcopy, used to diagnose lesion severity, has limited sensitivity ~70%

References: Saslow 2012, Dillner 2008
Shortcomings of Current Management
HPV and Low Grade Lesions

- No standard treatment exists
- Complicated, tedious surveillance recommendations
- Low adherence to surveillance protocol
  - Geographic relocations
  - Insurance migrations
  - High numbers lost to follow up
- Vaccines aimed at preventing HPV are significantly underutilized
  - 44% of parents in US rejecting vaccine recommendations
  - Only 1/3 of eligible girls in US are receiving vaccination
  - Offers no protection once virus is contracted
Shortcomings of Current Management

High Grade Lesions

- CIN 2/3 treated with invasive surgery
  - Most commonly LEEP

- Morbidities associated with the surgery are significant and particularly devastating in women of child bearing potential
  - Bleeding, infections, cervical stenosis, infertility, preterm labor, low birth weight infants

- Mean age of conization approaches mean age of first pregnancy

- 5-30% recurrence
  - Requires long term follow up
  - Unsatisfactory colposcopy
Cervical Conization Influences the Outcome in Pregnancy

- Increased risk of preterm delivery
- High impact on health care costs
- Relative risk of late miscarriages 4.0
Summary

• HPV related disease of cervix affects majority of women and risk of development of cervical cancer if not managed appropriately
  – 10 million women globally with high grade lesions
  – 30 million women globally with low grade lesions

• Current screening and surveillance of low grade lesions (CIN1) complicated with high risk of women lost to follow up and possible disease progression
  – Need for new treatments in women with associated high risk HPV related infections

• Need for new treatment options of high grade lesions (CIN 2)

Need for non-invasive, safe alternatives to ensure rapid clearance of HPV and lesions
A Randomized Phase 2b Study of HAL Photodynamic Therapy in Patients with Low/Moderate Grade Cervical Intraepithelial Neoplasia (CIN 1/2)

Peter Hillemanns, MD, PhD
Principal Investigator
Department of Gynecology and Obstetrics
University Hospital
Hannover, Germany
Objectives of Cevira Phase 2b Study

- To verify feasibility, efficacy and safety of the new Cevira photodynamic treatment in a placebo controlled multicenter Phase 2b study in patients diagnosed with CIN 1/2

- To define the optimal efficacy endpoint(s) and patient population(s) to enable design of further clinical program

- To determine the preferred dose of hexylaminolevulinate (HAL)
Cevira Fully Integrated Drug-Device

- Cevira ointment containing HAL applied into the device and placed on the cervix by the gynecologist

- Automatic photoactivation 5 hours after drug application

- Integrated light source delivers 100J/cm² of red (629nm) light photoactivation lasting 4.6 hours

- Patient removes device after completion of treatment
Phase 2b Clinical Trial End Points

- **Primary efficacy/Patient response**
  - Histology (central review)
  - Cytology
  - HPV DNA genotyping

- **Secondary efficacy**
  - Cytology
  - HPV DNA genotyping of 12 high-risk oncogenic subtypes

- **Safety assessments**
  - Local tolerance
  - Adverse events

3 months after last treatment
Histology, Cytology, HPV

6 months after last treatment
Cytology, HPV
Main Study Metrics

- Enrolled 262 patients (average age 27 years) with local histology confirmed CIN 1 or CIN 2 (safety population)
- 190 patients with CIN 1 (103) and CIN 2 (87) verified by central blinded review (efficacy population)
- 51% CIN 1 and 83% CIN 2 patients with positive HPV DNA status
- 50 CIN 1/2 patients with positive HPV 16/18 DNA status
- 1 or 2 treatments depending on results at 3 months
  - 52% of the patients received 2 treatments
- Patients enrolled at 23 centers in EU and US
Study Demonstrated a Clear Dose Response
5% is Optimal Dose

CIN 2 overall response 3 months after last treatment (n=87)

% responders

HAL 5%  p=0.01
HAL 1%  p=ns
HAL 0.2% p=ns
Placebo

P values versus placebo
Cevira Demonstrated Significant and Sustained Efficacy in CIN2 Patients after 6 months

CIN2 overall response 3 months after last treatment (n=40)

- HAL5%: High response rate
- Placebo: Lower response rate

p = 0.01

CIN2 overall response 6 months after last treatment (n=40)

- HAL5%: High response rate
- Placebo: Lower response rate

p = 0.02
Cevira Demonstrated Sustained Clearance of HPV including HPV 16/18 at 6 months

*12 oncogenic HPV subtypes
Cevira Showed a Superior Clearance of HPV 16/18 in the Overall Population

• Several HPV subtypes can cause precancerous lesions which lead to cervical cancer

• HPV 16 and 18 have the highest risks, accounting for
  – 70% of all cervical cancers
  – 50% of all high grade lesions
  – 25% of all low grade lesions

• Cevira showed superior clearance of high risk HPV 16/18 in the overall study population

• By clearing the virus rapidly, Cevira has the potential to significantly reduce the potential of progression to cervical cancer

HPV 16/18 clearance in CIN 1/2 patients 6 months after last treatment (n=50)
Cevira Tolerability and Acceptance

- No serious or systemic treatment related events were reported

- Treatment was well tolerated by the patients at all doses
  - Only self-limiting local events (e.g. discharge, discomfort, bleeding) were reported in 38% of the patients

- Several pregnancies reported during study
  - all normal full term deliveries

- High acceptance by patients and gynecologists
Summary of Results

• Cevira at the optimal dose demonstrated sustainable efficacy in CIN 2 patients
  – Significant sustained overall response
  – High and sustained clearance of high risk HPV 16/18

• Cevira at the optimal dose showed a clear effect in overall response and HPV 16/18 clearance in the CIN 1/2 study population, though not statistically significant

• The study confirmed the strong patient and gynecologist acceptability and safe use of Cevira

• The study forms an excellent basis for selecting patient populations and endpoints for further clinical development
Conclusion

Kjetil Hestdal, MD, PhD
President & CEO
Conclusion

• High unmet medical need for novel therapies to treat epidemic proportions of HPV/CIN populations

• Breakthrough technology allows for convenience and simplicity which can be integrated in even under-developed healthcare systems

• Results of the Phase 2b trial are significant and lay the foundation for the Phase 3 registration program
  – Significant overall response in CIN 2
  – High clearance of HPV, including highly oncogenic HPV 16/18
  – Excellent tolerability and high physician & patient acceptance

• Discussions underway to secure ideal global development and commercialization partner

• Photocure continues to deliver on the milestones as the evolution into a profitable specialty pharma company continues
Q & A
Moderated by K Hestdal