EVALUATION AND MANAGEMENT OF THE HIRSUTE PATIENT

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LEARNING OBJECTIVES

• Counsel patients concerning the differential diagnosis of hirsutism

• Devise an effective diagnostic scheme to evaluate patients with hirsutism

• Understand the therapeutic options for the treatment of hirsutism
COI

• Consulting for Longitude Capital; and Ansh Labs; and on the advisory board for GlobalPET Imaging.
SIGNS OF HYPERANDROGENISM IN WOMEN

• Dermatologic
  – Hirsutism
    – Acne
    – Alopecia

• Ovulatory dysfunction
  – DUB/AUB
  – Oligo‐amenorrhea
  – Oligo‐ovulatory eumenorrhea

• Virilization
  – Masculinization
  – Clitoromegaly
  – Severe hirsutism
  – Male‐pattern balding
Differential Diagnosis Among 873 Consecutive Untreated Patients Evaluated for Androgen Excess

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total #</th>
<th>% Prevalence</th>
<th>% Unbiased Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific disorders</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ASN</td>
<td>2</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>CAH</td>
<td>6</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>NCAH</td>
<td>18</td>
<td>2.06</td>
<td>1.60</td>
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<tr>
<td>HAIRAN</td>
<td>33</td>
<td>3.78</td>
<td>3.12</td>
</tr>
<tr>
<td>Disorders of exclusion</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PCOS</td>
<td>716</td>
<td>82.02</td>
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<tr>
<td>IH</td>
<td>39</td>
<td>4.47</td>
<td>4.68</td>
</tr>
<tr>
<td>HA+Hirsutism</td>
<td>59</td>
<td>6.75</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>873</td>
<td>100.00%</td>
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</tbody>
</table>

VIRILIZING OVARIAN TUMORS

• < 1% of all ovarian neoplasms
• 1/300-1/1000 of hirsutism cases
• Majority are palpable (> 5 cm)
• Low malignancy/mortality
• Pathology:
  Sertoli-Leydig cell/ androblastoma
  Granulosa-theca cell
  Adrenal-like (incl. lipoid cell)
  Hilar (thecal, leydig, mets)
THE SENS, SPEC, AND NPV & PPV OF A TOTAL T >250 NG/DL OR A DHEAS >6000 NG/ML FOR THE DETECTION OF AN ANDROGEN-SECRETING NEOPLASM (AAN)

At UAB, among 478 consecutive HA women, only one (0.2%) had an ovarian AAN

<table>
<thead>
<tr>
<th></th>
<th>SENS</th>
<th>SPEC</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total T &gt;250 ng/dL</strong></td>
<td>100%</td>
<td>98%</td>
<td>100%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>(1/1)</td>
<td>(467/477)</td>
<td>(467/467)</td>
<td>(1/11)</td>
</tr>
<tr>
<td><strong>DHEAS &gt;6000 ng/mL</strong></td>
<td>N/A</td>
<td>98%</td>
<td>100%</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>(468/478)</td>
<td></td>
<td>(468/468)</td>
<td></td>
</tr>
</tbody>
</table>

CLINICAL DATA ON 14 WOMEN WITH VIRILIZING ADRENAL TUMORS

- Two w/ adenomas and 12 w/ Ca
- 13 of 14 were either virilized (11) and/or Cushingoid (6)
- 10/14 had had hirstuism for ≤ 2 yrs
- 7/14 and 4/14 had onset of hirsutism after ages 30 and 50 yrs, resp.

DHEAS AND TOTAL T LEVELS IN PATIENTS WITH ADRENAL ASN

ADRENOCORTICAL STEROIDOGENESIS IN P450c21 DEFICIENCY

ENZYME DESIGNATION

Cholesterol side-chain cleavage CYP11A
17α-Hydroxylase CYP17
17,20-Lyase CYP17
21-Hydroxylase CYP17
11β-Hydroxylase CYP11B1
Aldosterone synthase CYP11B2
Aromatase CYP19
3β-Hydroxysteroid dehydrogenase 3βHSD
17β-Hydroxysteroid dehydrogenase 17βHSD
5α-Reductase 5αRed

Modified from Donahoe PK, Crawford JD: In Welch KJ et al, editors: Pediatric surgery, ed 4, vol 2, Chicago, 1986, Year Book Medical Publishers
THE 21-OH DEFICIENCY CONTINUUM

SW-CAH

SV-CAH w/ renin

SV-CAH w/ nl renin

NCAH < 8 y.o.

NCAH 8 - 18 y.o.

NCAH > 18 y.o.
## PREVALENCE OF 21-OH DEFICIENT NCAH AMONG HYPERANDROGENIC WOMEN

<table>
<thead>
<tr>
<th>Country</th>
<th>Total</th>
<th>NCAH</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA (NE)</td>
<td>139</td>
<td>2</td>
<td>Cobin et al, 1985</td>
</tr>
<tr>
<td>USA (NE)</td>
<td>116</td>
<td>16</td>
<td>Pang et al 1985</td>
</tr>
<tr>
<td>USA (NE)</td>
<td>164</td>
<td>4</td>
<td>Azziz &amp; Zacur 1989</td>
</tr>
<tr>
<td>USA (SE)</td>
<td>86</td>
<td>2</td>
<td>Azziz et al, 1993</td>
</tr>
<tr>
<td>USA (SW)</td>
<td>83</td>
<td>1</td>
<td>Chetkowsk at al, 1984</td>
</tr>
<tr>
<td>Canada</td>
<td>72</td>
<td>4</td>
<td>Innanen &amp; Vale 1990</td>
</tr>
<tr>
<td>Ireland</td>
<td>96</td>
<td>6</td>
<td>McLaughlin et al, 1990</td>
</tr>
<tr>
<td>France</td>
<td>400</td>
<td>24</td>
<td>Kuttenn et al, 1965</td>
</tr>
<tr>
<td>Italy (South)</td>
<td>372</td>
<td>15</td>
<td>Carmina et al, 1987</td>
</tr>
<tr>
<td>Italy (North)</td>
<td>85</td>
<td>1</td>
<td>Motta et al, 1988</td>
</tr>
<tr>
<td>Spain</td>
<td>270</td>
<td>6</td>
<td>Escobar-Morreale, 2008</td>
</tr>
<tr>
<td>India</td>
<td>60</td>
<td>3</td>
<td>Mithal et al, 1988</td>
</tr>
<tr>
<td>India</td>
<td>63</td>
<td>3</td>
<td>Khandekar et al, 1990</td>
</tr>
<tr>
<td>Jordan</td>
<td>so</td>
<td>5</td>
<td>Arnaout, 1992</td>
</tr>
<tr>
<td>Israel</td>
<td>170</td>
<td>14</td>
<td>Eldar-Geva et al, 1990</td>
</tr>
<tr>
<td>Overall</td>
<td>1956</td>
<td>102</td>
<td></td>
</tr>
</tbody>
</table>
PROBABILITY OF 21-OH DEFICIENT NCAH ACCORDING TO STIMULATED 17-HP LEVEL

- <10 ng/ml (30 nmol/L) < 2%
- 10-15 ng/ml (30-45 nmol/L) 20-60%
- 16-200 ng/ml (>45 nmol/L) > 96%
- >200 ng/mL (600 nmol/L) < 10%
### BASAL 17-HP LEVELS IN 308 NCAH PATIENTS

<table>
<thead>
<tr>
<th>No.</th>
<th>% of NCAH Subjects</th>
<th>Basal 17-HP Level</th>
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</thead>
<tbody>
<tr>
<td>36</td>
<td>11.7%</td>
<td>&lt;2 ng/mL</td>
</tr>
<tr>
<td>28</td>
<td>9.0%</td>
<td>2-3 ng/mL</td>
</tr>
<tr>
<td>39</td>
<td>12.7%</td>
<td>3-4 ng/mL</td>
</tr>
<tr>
<td>91</td>
<td>29.5%</td>
<td>4-10 ng/mL</td>
</tr>
<tr>
<td>114</td>
<td>37.0%</td>
<td>&gt;10 ng/mL</td>
</tr>
</tbody>
</table>

NCAH Multicenter Study Group (unpublished)
SPECIFICITY: BASAL 17-HP LEVELS IN 8 NORMO-OVULATORY HEALTHY WOMEN

HAIRAN Syndrome

• Features:
  – HyperAndrogenic
  – Insulin Resistant
    • Basal INS > 50-80 µU/mL, or
    • Peak stimulated INS > 300-500 µU/mL
  – Acanthosis Nigricans

• Metabolic Syndrome

• Distinct entity?
  – Form of lipodystrophy
  – Variant of PCOS?
IDIOPATHIC HIRSUTISM

• Define strictly:
  – No evidence of increased circulating androgen levels
  – Normal ovarian morphology
  – Regular ovulation (and not just regular menstrual cycles)

• Often familial, although not more than other disorders
• May be due to increased peripheral utilization or sensitivity to androgens
• May reflect inadequate laboratory analysis
• Generally no more than 5% of hirsute women

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Phenotypes</th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Hirsutism/HA</td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Ovulatory Dysfunction</td>
<td>√</td>
<td></td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Polycystic ovaries</td>
<td>√</td>
<td></td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>NIH 1990*</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
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<tr>
<td>Rotterdam 2003*</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>AE-PCOS 2006*</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Always exclude related/similar/mimicking disorders (17-HP, TSH, Prl)
ROTTERDAM 2003 AND AE-PCOS 2006 ARE EXPANSIONS OF NIH 1990
HYPERANDROGENISM IN PCOS IS ASSOCIATED WITH RISK OF METABOLIC SYNDROME

Age-adjusted prevalence of MS is higher in all hyperandrogenic phenotypes of PCOS, compared to the non-hyperandrogenic PCOS phenotype and to controls.

-insulin resistance

Hyperinsulinemia

Hepatic SHBG suppression

Hyperandrogenism

Hepatic ShBG suppression

LH receptor

Insulin receptor

Ovarian theca stimulation

Obesity

Genetic syndromes

Insulin post-receptor abnormalities

Adipose tissue dysfunction

Anti-insulin-receptor antibodies
SEVERITY OF MENSTRUAL DYSFUNCTION PREDICTS DEGREE OF IR IN 494 PCOS

PREVALENCE OF GLUCOSE INTOLERANCE & TYPE 2 DM IN PCOS

**Ehrmann et al. Diabetes Care 1999; 22:141
*Legro et al. J Clin Endocrinol Metab 1999; 84:165
*Azziz et al. J Clin Endocrinol Metab 2001; 86:1626

- University of Chicago: 122
- Penn State Univ: 144
- Mt Sinai: 110
- Rezulin Collab Grp: 408

TOTAL: 784
PREDICTIVE VALUE OF A FASTING GLUCOSE VALUE ON OGTT STATUS

Legro et al. J Clin Endocrinol Metab 1999;84:165-9
The Diagnosis of Polycystic Ovary Syndrome during Adolescence

Selma F. Witchel\textsuperscript{a} Sharon Oberfield\textsuperscript{b} Robert L. Rosenfield\textsuperscript{c} Ethel Codner\textsuperscript{d} Andrea Bonny\textsuperscript{e} Lourdes Ibáñez\textsuperscript{f} Alexia Pena\textsuperscript{g} Reiko Horikawa\textsuperscript{h} Veronica Gomez-Lobo\textsuperscript{i} Dipesalma Joel\textsuperscript{j} Hala Tfayli\textsuperscript{k} Silva Arslanian\textsuperscript{l} Preeti Dabadghao\textsuperscript{m} Cecilia Garcia Rudaz\textsuperscript{n} Peter A. Lee\textsuperscript{o}

\textsuperscript{a}Department of Pediatrics, Children's Hospital of Pittsburgh, Pittsburgh, Pa., \textsuperscript{b}Department of Pediatrics, Morgan Stanley Children's Hospital, New York, N.Y., and \textsuperscript{c}Section of Adult and Pediatric Endocrinology, Diabetes, and Metabolism, The University of Chicago Pritzker School of Medicine, The University of Chicago Medical Center, Chicago, Ill., USA; \textsuperscript{d}Endocrinología y Diabetes Infantil, Instituto de Investigaciones Materno Infantil, Universidad de Chile, Santiago, Chile; \textsuperscript{e}The Ohio State University, Nationwide Children's Hospital, Columbus, Ohio, USA; \textsuperscript{f}Hospital Sant Joan de Déu, University of Barcelona, Esplugues, Spain; \textsuperscript{g}Department of Paediatrics, The University of Adelaide, Women's and Children's Hospital, Adelaide, S.A., Australia; \textsuperscript{h}Division of Endocrinology and Metabolism, National Center for Child Health and Development, Tokyo, Japan; \textsuperscript{i}Pediatric and Adolescent Obstetrics/Gynecology, Washington Hospital Center/Children's National Medical Center, Clinical Obstetrics/Gynecology, Georgetown University, Washington, D.C., USA; \textsuperscript{j}Botswana-Baylor Children's Clinical Centre of Excellence, Princess Marina Hospital, Gaborone, Botswana; \textsuperscript{k}Department of Pediatrics and Adolescent Medicine, American University of Beirut Medical Center, Beirut, Lebanon; \textsuperscript{l}Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., USA; \textsuperscript{m}Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India; \textsuperscript{n}Department of Paediatric Diabetes and Endocrinology, Monash Children’s Medical Centre, Clayton, Vic., Australia; \textsuperscript{o}Penn State College of Medicine, Milton S. Hershey Medical Center, Hershey, Pa., USA.
EVALUATION OF THE HYPERANDROGENIC/HIRSUTE PATIENT

• HISTORY:
  Drugs/skin irritants/menses/onset and progression/change in weight/change in head or extremity size/family

• PHYSICAL:
  Hair pattern and type/galactorrhea/acanthosis/cushingoid features/clitoromegaly or virilization/regional distribution of obesity
EVALUATING FOR CLINICAL HYPERANDROGENISM: THE MODIFIED F-G (mFG) SCORE
EVALUATING FOR CLINICAL HYPERANDROGENISM: THE MODIFIED F-G (mFG) SCORE

Yildiz et al, Hum Reprod Update 2010;16:51–64
Cluster analysis indicates that an mFG score of ≥3 may indicate abnormal terminal hair growth.
THE PREVALENCE OF AN ANDROGEN EXCESS DISORDER IN WOMEN WITH MINIMAL UNWANTED HAIR GROWTH

• 228 patients with minimal unwanted hair growth (\(mF-G \leq 5\))

• 54% demonstrated an AE disorder
  – 50%: PCOS
  – 2%: HAIRAN Sx
  – 2%: NCAH

• And it's not only in those subjects with abnormal menses:
  – 65% of those with menstrual irregularities had an AE disorder
  – 22% of those with normal menstrual function had an AE disorder

Souter et al, AJOG. 2004;191:1914–20
LABORATORY EVALUATION OF THE HIRSUTE OR POTENTIALLY HYPERANDROGENIC PATIENT

- **TSH & PRL**
  - In oligo-ovulatory patients, to R/O other causes of ovulatory dysfunction

- **17-HP**
  - To R/O 21-OH deficient NCAH

- **d. 22-24 P4 level**
  - In hirsute eumenorrheic women, 40% of which are anovulatory

- **Total & free T (and DHS AND A4?)**
  - Most importantly, in evaluating non-hirsute or minimally hirsute patients to R/O Androgen Excess
  - **MUST USE HIGH-QUALITY WELL-REFERENCED ASSAY**
ANDROGEN LEVELS IN PCOS: LIMITED SENSITIVITY OF MEASURING ONLY TOTAL T

• In NIH 1990 (classic) PCOS patients, using high quality sensitive assays (for TT, FT & DHEAS) ~75% demonstrate HA

• Alternatively, in NIH 1990 (classic) PCOS patients if TT alone is measured (using a high quality RIA) then only 33% of demonstrate HA

• ~50% of PCOS phenotype studies assessed only TT, usually using a chemiluminescent platform assay, so one can expect that in these studies detection rates for HA will be well less than 30%

Prevalence of specific combinations of androgen levels in NIH 1990 PCOS

<table>
<thead>
<tr>
<th>Total T</th>
<th>Free T</th>
<th>DHEAS</th>
<th>% patients with PCOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>24.7%</td>
</tr>
<tr>
<td>↑</td>
<td>↑</td>
<td>Normal</td>
<td>20.4%</td>
</tr>
<tr>
<td>Normal</td>
<td>↑</td>
<td>Normal</td>
<td>20.0%</td>
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<tr>
<td>↑</td>
<td>Normal</td>
<td>↑</td>
<td>13.8%</td>
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<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>8.7%</td>
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<tr>
<td>Normal</td>
<td>↑</td>
<td>↑</td>
<td>8.5%</td>
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<tr>
<td>↑</td>
<td>Normal</td>
<td>↑</td>
<td>2.2%</td>
</tr>
<tr>
<td>↑</td>
<td>Normal</td>
<td>↑</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

WHY ARE ANDROGEN LEVELS “NORMAL” IN SOME PATIENTS WITH AE?

• 20% of patients with AE/PCOS have normal androgen levels
• The measurement of androgens is notoriously difficult, particularly in women
• The “normal” range for an assay kit is often established by the manufacturer and not the user; and are often established using women not clearly “normal”
• There is no tight endocrine regulation of androgen levels in women (or men), permitting a wide variability in androgen levels among individuals
TREATMENT OF ANDROGEN EXCESS

• Goals include treatment & prevention of:
  – Dermatologic disorders (hirsutism, acne, alopecia)
  – Ovulatory & menstrual dysfunction (DUB, endometrial hyperplasia or Ca)
  – Metabolic abnormalities, incl. dyslipidemia, glucose intolerance & obesity
  – Infertility

• Optimum treatment is generally combination therapy
MEDICAL THERAPY OF ANDROGEN EXCESS: Source suppression

• **Ovarian:**
  – OCPs
  – Estrogen/Progestin
  – Metformin/Thiazolidinediones
  – GnRH-a

• **Adrenal:**
  – Dex/Prednisone

• **Both:**
  – Ketoconazole
COMBINATION ORAL CONTRACEPTIVE

↑ SHBG

↓ LH

↑ Testosterone Binding Capacity

↓ Testosterone Production

↓ Free Testosterone Levels
MEDICAL THERAPY OF ANDROGEN EXCESS:
Androgen blockade

- Spironolactone
- Flutamide
- Cyproterone acetate
- Finasteride
ANTIANDROGENS IN HIRSUTISM

**Ferriman-Gallwey score**

- Flutamide
- Spironolactone
- Finasteride
- Placebo

**Hair shaft diameter**

*P<0.01 placebo vs. other groups

*Moghetti et al. J Clin Endocrinol Metab 2000; 85:89-94*
HIRSUTISM SCORE BEFORE AND AFTER TREATMENT WITH DIANE-35 OR DIANE-35 + FINASTERIDE IN PATIENTS WITH IH OR PCOS

**IH**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
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</thead>
<tbody>
<tr>
<td>Diane-35</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Diane-35 + finasteride</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

**PCOS**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diane-35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diane-35 + finasteride</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*P < .005 vs. basal values; †P < .002 vs. basal values; ‡P < .05 vs. Diane-35 at the respective time point

*Tartagni et al. Fertil Steril 73:718, 2000*
LONG-TERM OUTCOME OF HIRSUTISM TREATMENT WITH AN OCP + SPIRONOLACTONE* COMBINATION IN 138 WOMEN WITH PCOS, ACCORDING TO INITIAL mFG SCORE

*OCP = Mostly 35 mg Ethinyl Estradiol and 1 mg Ethynodiol Diacetate; Spironolactone = 100mg/d for initial mFG 3-7; or 200 mg/d for initial mFG>8

Ezeh, unpublished
METFORMIN THERAPY IN PCOS

• Metformin is an agent that acts indirectly and modestly to:
  – Improve ovulation
  – Reduce long-term metabolic complications
METFORMIN VS. DIANE NOVA IN OBESE PCOS: A 6 MOS RANDOMIZED STUDY

*Metformin administered as 1000 mg/d x 3 mos, then 2000 mg/d x 3 mos

Morin-Papunen et al. J Clin Endocrinol Metab 2000;85:3161
TREATMENT OF ANDROGEN EXCESS-RELATED DERMATOLOGIC SYMPTOMS: PROGNOSIS

In general, we see the following sequence of improvement in clinical symptoms:

- ACNE (2-8 weeks)
- OLIGO-OVULATION (2-6 mos.)
- HIRSUTISM (3-8 mos.)
- ALOPECIA (6-18 mos.)
TREATMENT OF ANDROGEN EXCESS-RELATED HIRSUTISM: Mechanical/cosmetic

- Plucking: No!
- Waxing: No!
- Shaving
- Bleaching
- Chemical depilators
- Electrolysis
- Lasers

Must be combined with medical suppression for optimum results
PHYSICIAN’S GLOBAL ASSESSMENT OF THE EFFICACY OF EFLORNITHINE HCL CREAM, 13.9%: POOLED ANALYSIS

58% of subjects showed improvement

*Clinical success as defined by protocol

**P = 0.007

*** P = 0.001
THANK YOU