Cardiovascular Adverse Events

- Arrhythmia
- Bradycardia
- Tachycardia
- Dizziness
- Palpitations
- Syncope

Prospectively coded; HARTS Dictionary

Comparison of Frequency of Cardiovascular AEs Potentially Related to Hyperkalemia

- Treatment groups
  - Yasmin vs. Marvelon (Desogen®)
  - Yasmin vs. placebo
  - E2/DRSP 3mg vs E2
- Frequency of these AEs in subjects with hyperkalemia

Comparison of Frequency of Selected Cardiovascular Adverse Events (Pooled Data)

Adverse Event	DRSP 3 mg + E2 or EE[a] (N=2781)	DRSP 3 mg[b] (N=28)	Estradiol[c] (N=223)	Marvelon®[d] (N=857)	Placebo[e] (N=130)
Arrhythmia	0.1%	0%	0%	0.5%	0.8%
Bradycardia	0%	0%	0%	0%	0%
Dizziness	3%	4%	4%	5%	2%
Palpitations	0.8%	0%	2%	0.2%	2%
Syncope	0.3%	0%	0.4%	0.2%	0%
Tachycardia	0.5%	7%	0%	0.2%	0%

DRSP = drospirenone; E2 = estradiol; EE = ethinyl estradiol; N = total number of subjects.
[a]Data from Protocols 96049, 97036, 96097, 93044, and 92052.
[b]Data from Protocol 303063.
[c]Data from Protocols 96097.
[d]Data from Protocols 93044 and 92052.
[e]Data from Protocol 97036.

Interpretation of Cardiovascular Adverse Events

1. CV adverse events were equally distributed among controls and DRSP/combination groups

2. No evidence of link between hyperkalemia and cardiovascular adverse events in DRSP-treated subjects

Conclusion

Yasmin did not present a risk for the occurrence of cardiovascular adverse events potentially related to hyperkalemia

New Initiatives

- To better understand the risk factors in the target population
  - Review of the literature relating to spironolactone

Gynecological Applications/Experience with Spironolactone

- Applications based upon antimineralocorticoid & antiandrogenic properties
  - Polycystic Ovarian Syndrome
  - Hirsutism
  - PMS/PMDD (ACOG Practice Bulletin, Number 15, April 2000)
  - Acne
- 1.2 million Rxs/131,000 patients treated for gynecological and androgen-related disorders*
- Clinical experience demonstrates safety at doses up to 200mg

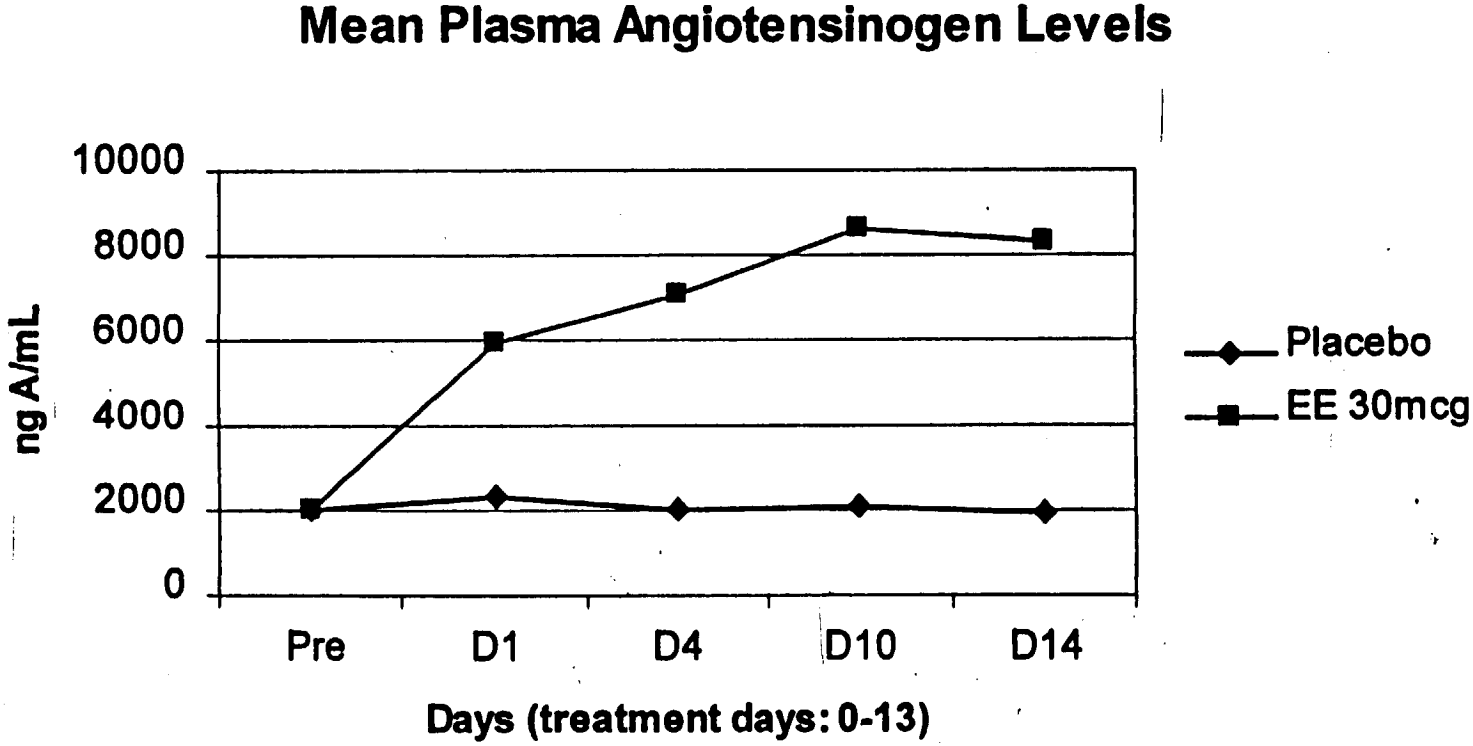
** IMS data*

Literature Review on Spironolactone

- 56 publications (Hyperandrogenic conditions)
- ~1600 patients (ages 3-60 yrs)
- Spironolactone 40-229 mg/day
- Electrolyte alterations
  - 200mg/day: 1 case suspect hyperkalemia (by symptoms)
  - 100mg/day: 1 case elevated potassium (6.2 nmol/L)

***Criteria**: published 1985-2000; English language; terms: spironolactone and PCOS, hirsutism, acne; case reports and studies*

Angiotensinogen Levels

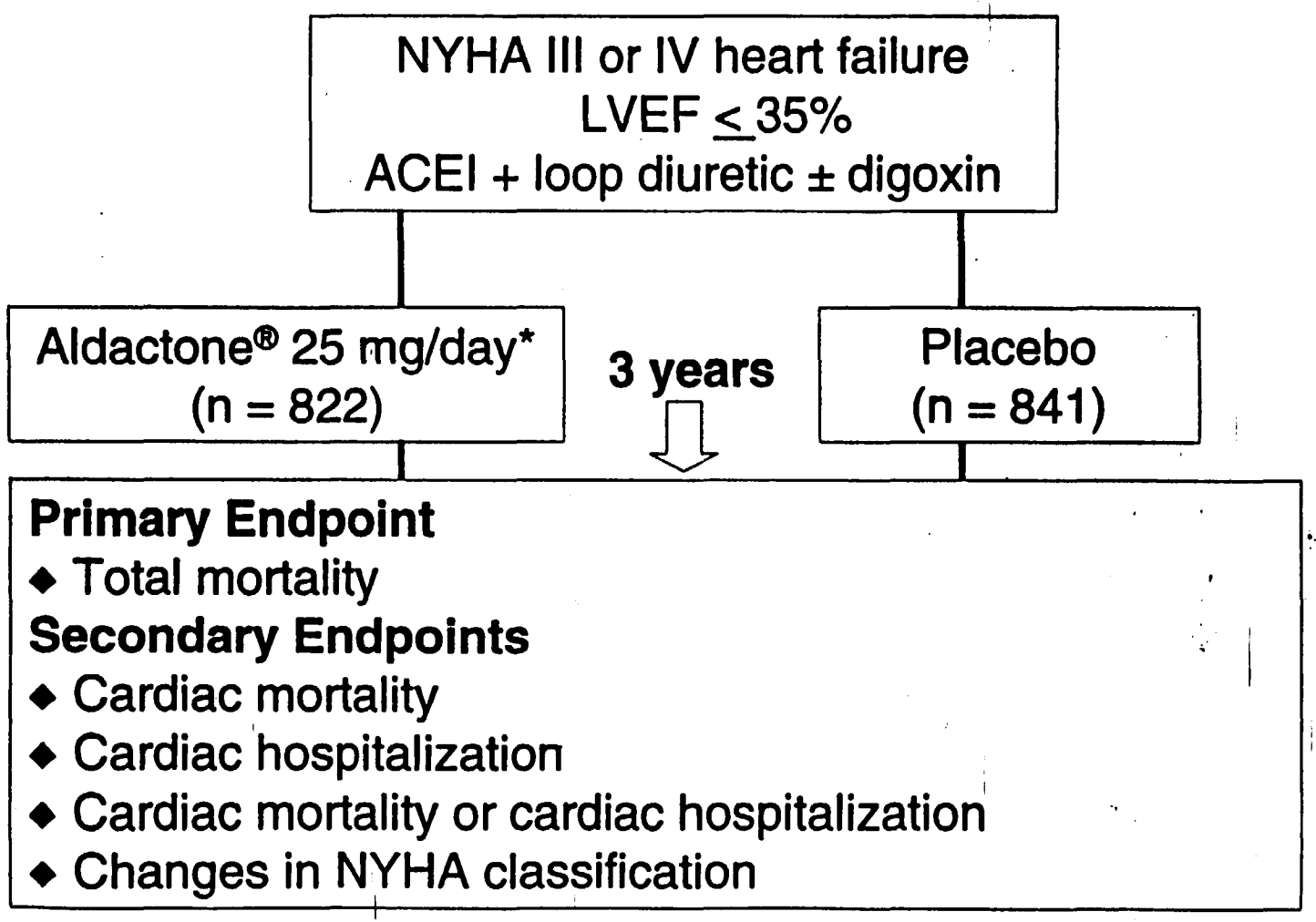


Data on file. EE-N=9-10, Placebo- N=17 post menopausal women

Conclusion

- Spironolactone is a widely accepted, well-tolerated treatment for gynecological and androgen disorders
  - Used for extended periods, i.e., years
  - Used in high doses, 100-200 mg/day
- Antimineralocorticoid activity offers potential to counter estrogen's effect on RAAS/aldosterone
- Theoretical benefits for general OC population outweigh theoretical risk in contraindicated patient segment

RALES: Study Design



Pitt et al. *N Engl J Med.* 1999;341:709.

*Protocol used a starting dose of 25 mg/day whereas the mean daily dose was 26 mg.

RALES: Baseline Patient Characteristics

	Placebo (n=841)	Spironolactone (n=822)
Age (years)	65 ± 12	65 ± 12
Race (% of patients)		
Caucasian	86	87
Gender (number, %)		
Male	614 (73)	603 (73)
Female	227 (27)	219 (27)
Blood Pressure (mm Hg)		
Systolic	122 ± 20	123 ± 21
Diastolic	75 ± 11	75 ± 12
Heart rate (beats/min)	81 ± 15	81 ± 14
New York Heart Association Class (number, %)		
II	3 (0.4)	4 (0.5)
III	581 (69)	592 (72)
IV	257 (31)	226 (27)

Pitt et al. *N Engl J Med.* 1999;341:709.

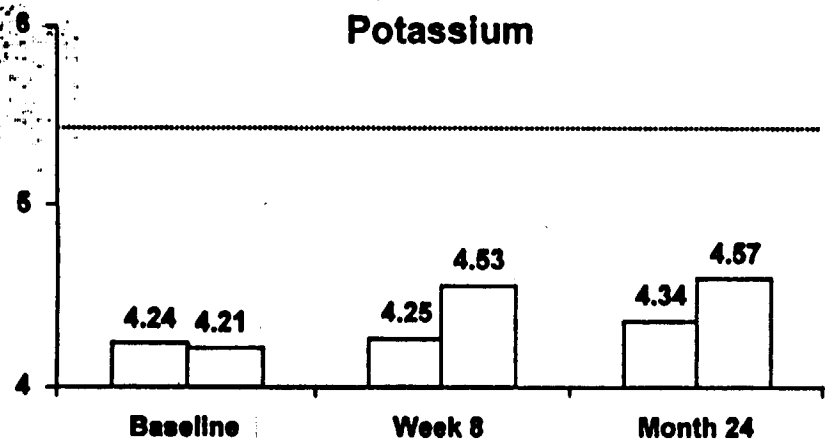
RALES: Baseline Patient Characteristics

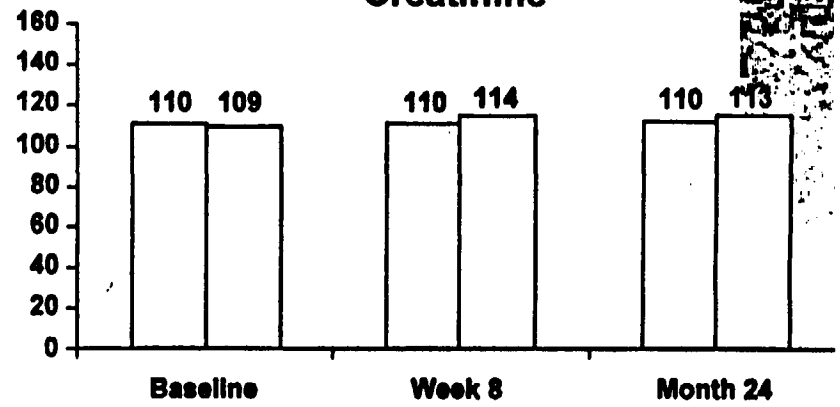
	Placebo (n=841)	Spironolactone (n=822)
LVEF (%)	25.2 ± 6.8	25.6 ± 6.7
Cause of heart failure (number, %)		
Ischemic	453 (54)	454 (55)
Nonischemic	386 (46)	368 (45)
Medication (% of patients)		
Loop diuretics	100	100
ACE inhibitors	94	95
Digitalis	72	75
Aspirin	37	36
Potassium supplements	27	29
β-blockers	10	11
Mean dose of ACEI (mg/day)		
Captopril	62.1	63.4
Enalapril	16.5	13.5
Lisinopril	13.1	15.5

Pitt et al. *N Engl J Med.* 1999;341:709.

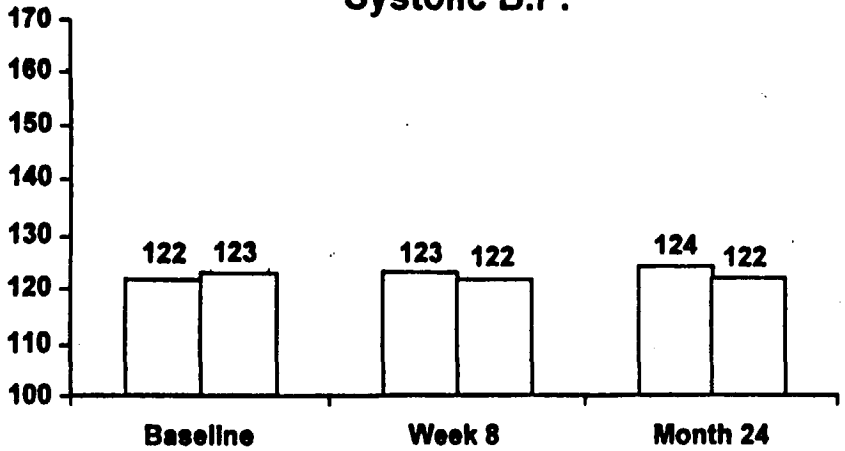
Yasmin
NDA 21-098

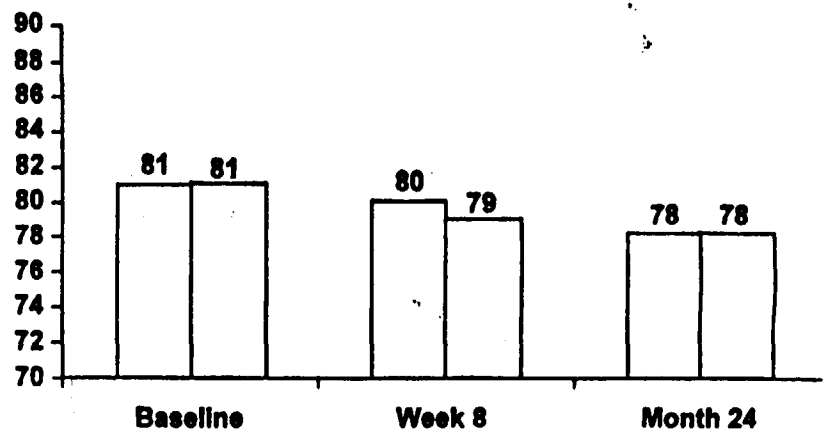
Safety Parameters





Placebo Spironolactone





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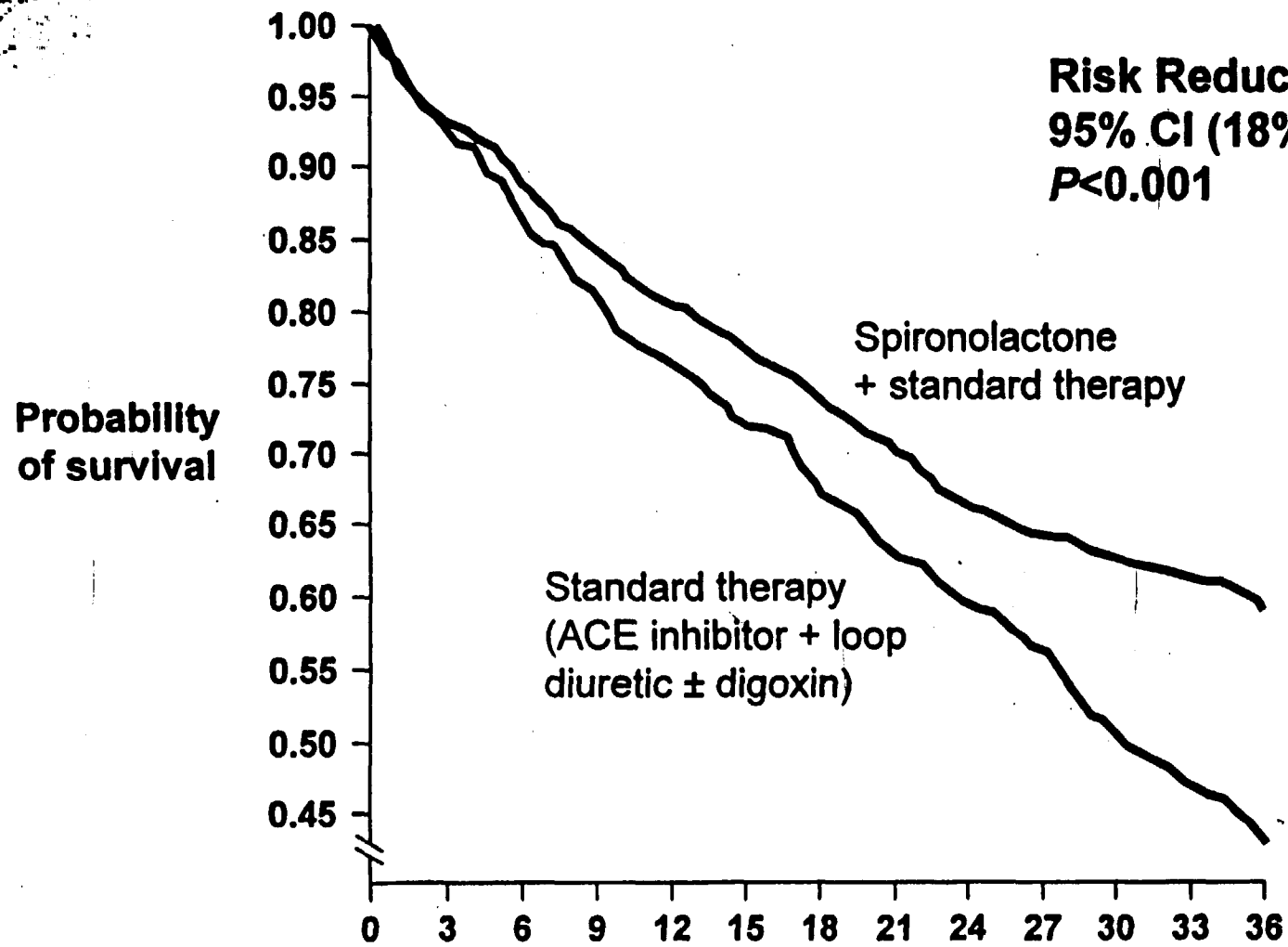
RALES: All-Cause Mortality



Pitt et al. *N Engl J Med.* 1999.

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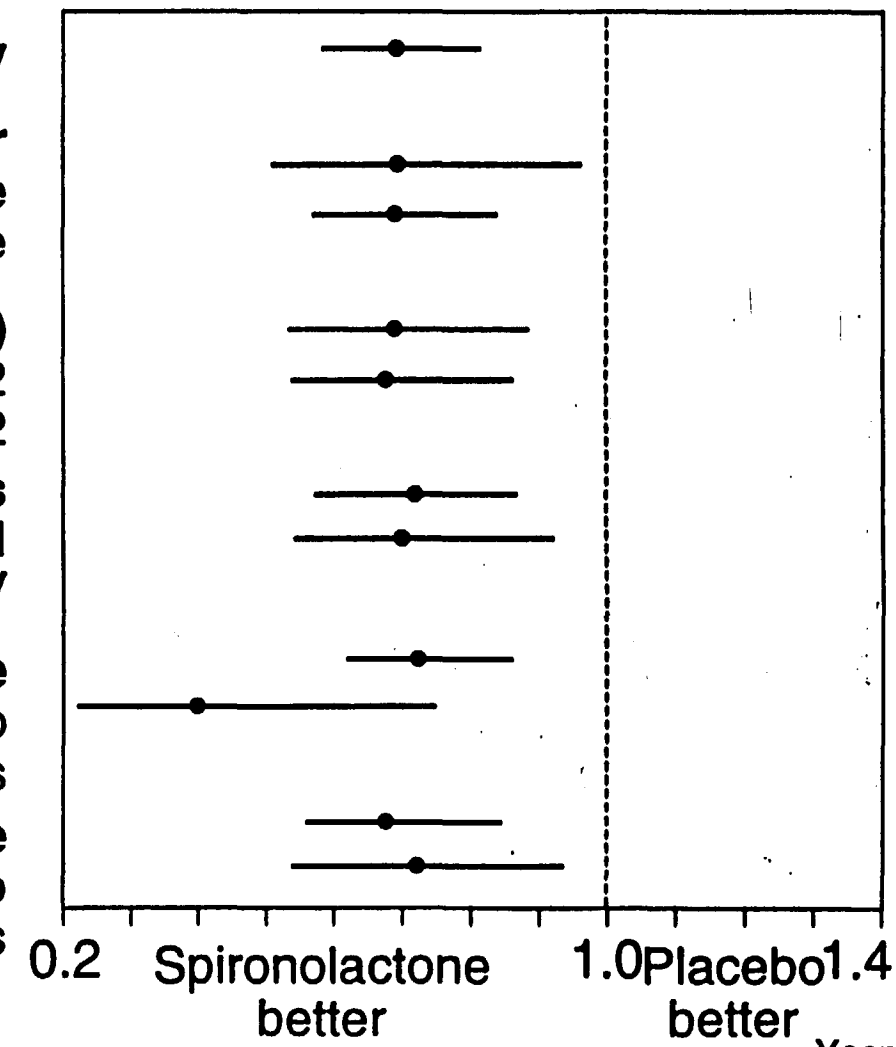
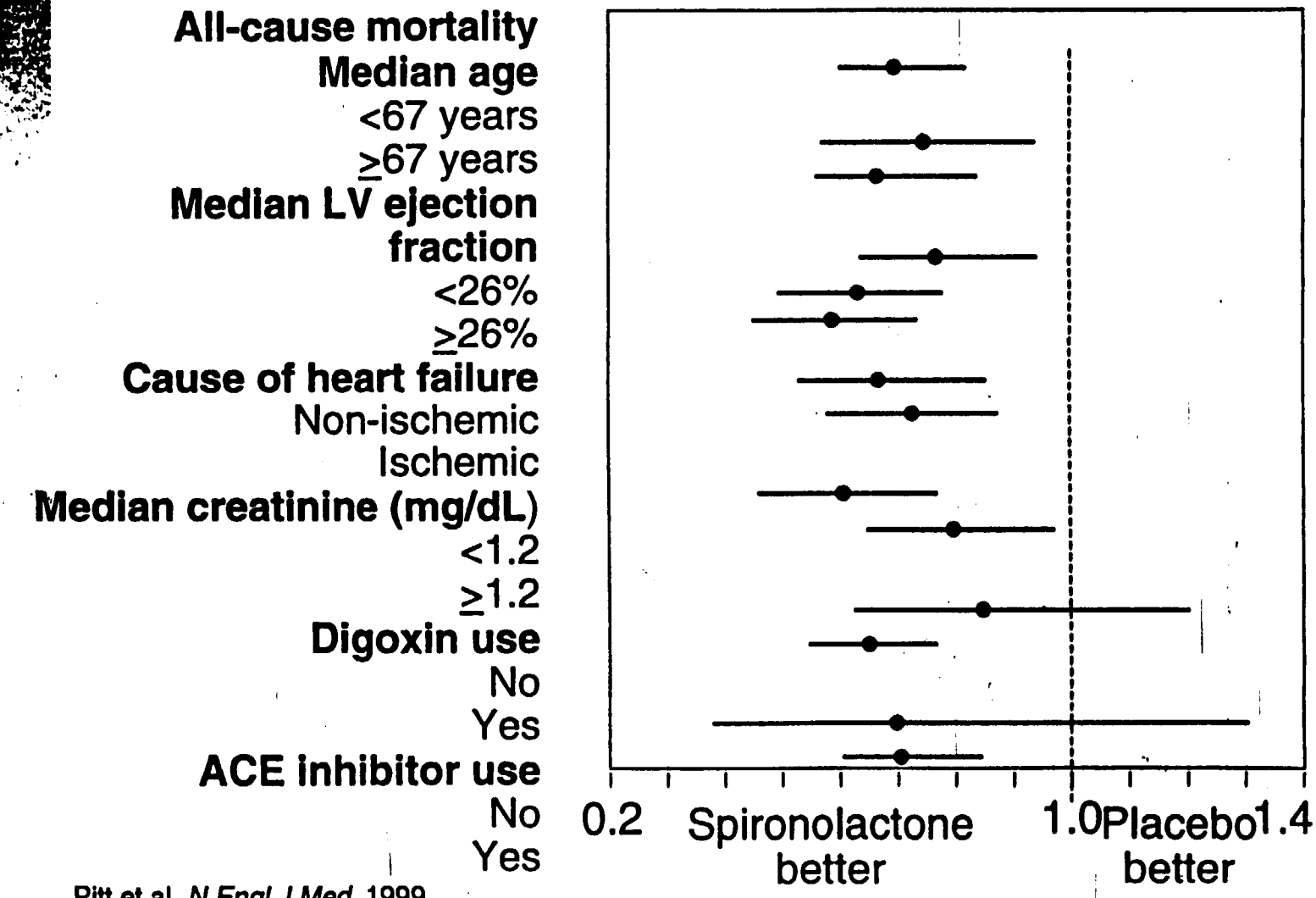
RALES: Relative Risk in Subgroups



Pitt et al. *N Engl J Med.* 1999.

Yasmin
NDA 21-098

RALES: Relative Risk in Subgroups

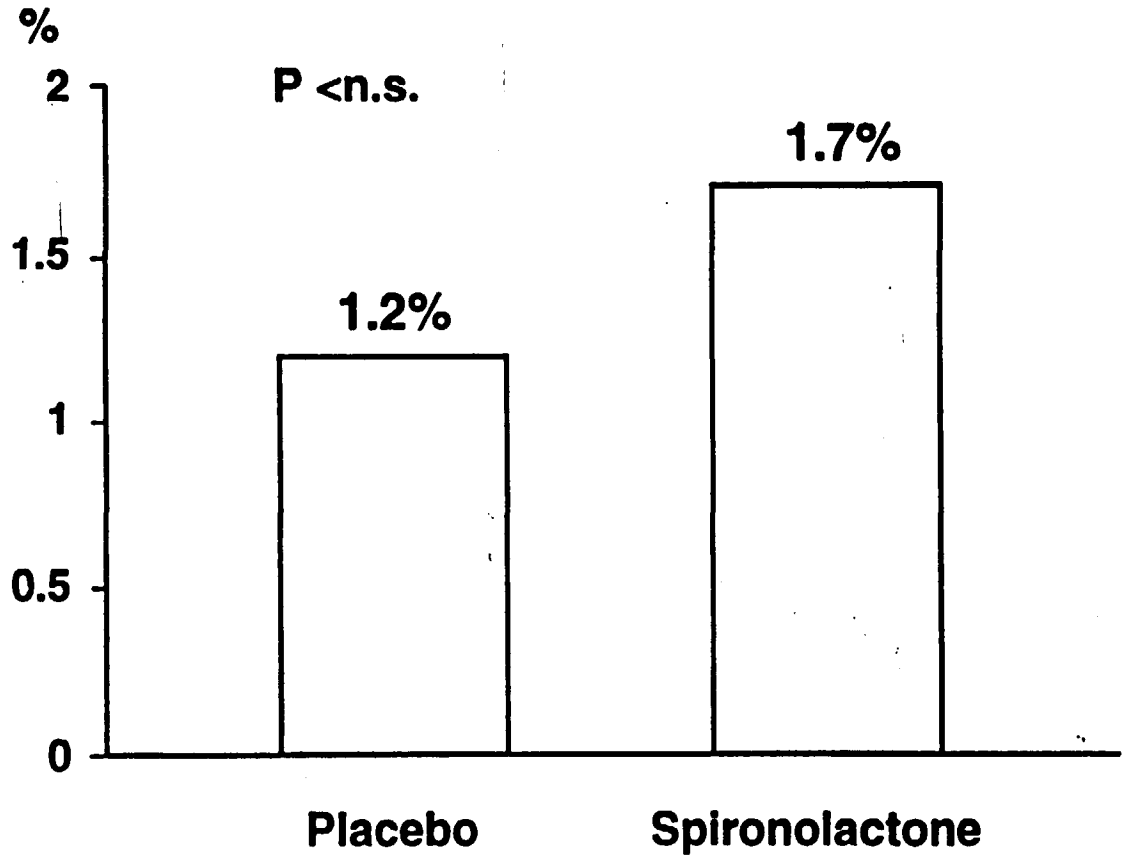


Pitt et al. *N Engl J Med.* 1999.

Yasmin
NDA 21-098

Adverse Reactions

Serious Hyperkalemia ≥ 6.0 mmol/L



Aldosterone Receptor Antagonism

- Cardiovascular Benefits:
  - Increases sodium excretion & prevents edema*
  - Prevents hypokalemia*
  - Prevents perivascular & mycardial fibrosis*
  - Reverses myocardial hypertrophy*
  - Improves diastolic function*
  - Improves endothelial function & nitric oxide availability*
  - Improves vascular compliance**
  - Decreases systolic & diastolic blood pressure*
  - Improves myocardial norepinepherine uptake*
  - Improves heart rate variability*
  - Improves baroreceptor function*
  - Decreases ventricular ectopic activity*
  - Decreases plasminogen activator inhibitor (PAI-1)*
  - Decreases cerebral infarct size**
  - Prevents renal fibrosis & urinary protein excretion**
  - Improves mortality & morbidity in patients with severe heart failure maintained on an ACE-I.*

*Preclinical & clinical data

**Preclinical data

Hypokalemia

- *Reference: Cohn JN, Kowey PR, Whelton PK, Prisent M; Arch Intern Med, Sept. 11, 2000*
  - "Potassium depletion is one of the most common electrolyte abnormalities in clinical practice"
  - Recent published guidelines recommend efforts to increase serum potassium levels in the general population

Mechanism-Based Theoretical Risk/Benefit

- Potassium Retention/Aldosterone Antagonism

Risk	Benefit
Hyperkalemia	**Maintain Potassium Pool**
	Gynecologic
	Cardiovascular

Mechanism-Based Theoretical Risk/Benefit

Risk	Population Estimate	Benefit	Population Estimate	
Hyperkalemia	2348	Hypokalemia	1,886,000	①
		CHF	37,000	②
		Hypertension	1,540,000	
		PCOS	125,000	
		Hirsutism	92,000	
Total	2348		3,680,000	

① *NHANES*

② *NDTI*

Overall Conclusions

1. **We believe that the theoretical benefits far outweigh any theoretical risk.**

Overall Conclusions (continued)

2. Yasmin did not present a risk for hyperkalemia or for the occurrence of cardiovascular adverse events potentially related to hyperkalemia in the OC population including use in patients:

   - On NSAIDs
   - On ACE inhibitors
   - With mild-moderate renal disease

Overall Conclusions (continued)

3. We believe that conducting any additional study prior to the approval of Yasmin would not provide any further insight into:
   - Risk of hyperkalemia
   - Guide for risk management programs for contraindicated populations.

Active Surveillance Goal

Develop a cohort of OC users to:

- Assess oral contraceptive prescribing to women with hepatic or renal dysfunction
- Assess the occurrence of clinical events potentially related to hyperkalemia with Yasmin in comparison to other oral contraceptives
- Monitor breakthrough pregnancies for fetal/child malformations that occur with Yasmin

Oral Contraceptive Prescribing

- Use claims data to identify women with hepatic and/or renal dysfunction in the six months preceding the oral contraceptive prescription
- Prepare full case report summaries derived from screening claims histories for all such occurrences

Oral Contraceptive Prescribing

- Prevalence estimates from a preliminary inquiry of 1998 claims data for more than 350,000 women ages 15-44
  - Renal dysfunction = 1.2/1000
  - Hepatic dysfunction = 3.4/1000
  - Renal dysfunction and oral contraceptive use = 14/100,000
  - Hepatic dysfunction and oral contraceptive use = 56/100,000

Adverse Clinical Outcomes Monitoring

- Identify the cohort of women taking Yasmin and a comparison cohort of oral contraceptive users from a large administrative database
- Compare outcomes in the two groups over 2-3 years, including
  - sudden death
  - clinically manifest arrhythmias
  - electrolyte disturbances
  - hospitalizations (not clearly associated with an unrelated chronic condition, infection, or trauma)
- Develop full case report summaries for each occurrence

Statistical Analyses

Goals can be achieved

- Inappropriate prescribing
  - Can be detected within the first year if the incidence is 1/1000; >95 percent chance of detection by the end of the study with incidences of 1/10,000
- Adverse clinical outcomes
  - >90 percent power for detecting a relative risk of 1.6 or higher in the outcomes related to hyperkalemia
- Pregnancy outcomes
  - >90 percent power to demonstrate a doubling of congenital malformation risks

Education and Outreach

Objectives

- Educate physicians on appropriate patient types
  - Minimize use of Yasmin in at-risk patient populations
- Help healthcare professionals properly educate patients on appropriate contraceptive choices

Education and Outreach

Strategy

- Focus on gatekeepers
  - Physician
  - Nurse/NPA
  - Pharmacists
- Education strategy
  - Focus on the pharmacology of DRSP to educate physicians on why certain patient types are at risk

Education and Outreach

Tactics

- Physician & nurse education
  - Berlex sales representative based
    - Special representative training
      - CD-ROM based
      - Proficiency testing
  - DRSP pharmacology detail aids:
    - Focus on antimineralocorticoid properties and potassium levels
    - Focus on contraindicated patients

Education and Outreach

Tactics (continued)

- CME
  - 200 symposia nationwide (Lunch & Learn, Grand Rounds, Regional Meetings)
- Publication on pharmacology & at-risk patients in physician journals
- Direct mail follow-up to rep detailing
    - Reminding physicians on pharmacology and at-risk patients

Education and Outreach

Pharmacist

- CME brochure on pharmacology and the at-risk patient
- Rep detail
- Publication on pharmacology

Education and Outreach Evaluation

- Communication testing
- Prescribing tracking
- Awareness tracking
  - Tracking of awareness of at-risk patients and the pharmacology of DRSP

Concluding Remarks

Based on the results of the analysis of serum potassium concentrations, use of DRSP either alone or concomitantly with NSAIDS or ACE inhibitors was not associated with the risk of hyperkalemia. In addition, these results indicate that mild or nonprogressive moderate renal insufficiency did not cause hyperkalemia in subjects receiving DRSP.

Questions

- Does the Phase IV program, including the education aspect as outlined, address the Division's request?

Questions

- Based on the additional data, does the Division concur that no additional studies are needed prior to approval?

Teleconference Meeting Minutes

Date: July 10, 2000 **Time:** 12:30-1:00 pm **Location:** Parklawn; 17-B45

NDA 21-098 **Drug:** Yasmin® 28 Tablets (drospirenone and ethinyl estradiol)

Indication: Oral Contraception

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Action Status

Meeting Chair: Dr. Florence Houn

External Lead: Ms. Nancy Velez

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Florence Houn, M.D., M.P.H., Office Director, Office of Drug Evaluation III (ODE III; HFD-103)
Susan Allen, M.D., M.P.H., Director, Division of Reproductive and Urologic Drug Products, (DRUDP; HFD-580)
Marianne Mann, M.D., Deputy Director, DRUDP (HFD-580)
Dan Shames, M.D., Team Leader, DRUDP (HFD-580)
Scott Monroe, M.D., Medical Officer, DRUDP (HFD-580)
Terri Rumble, B.S.N, Chief, Project Management Staff
Jeanine Best, M.S.N., R.N., Regulatory Project Manger, DRUDP (HFD-580)

External Attendees:
Berlex Laboratories, Inc.
Nancy Velez, Manager, Drug Regulatory Affairs
June Bray, Vice President, Regulatory Affairs
Sharon Brown, Associate Director, Regulatory Affairs
Nancy Konnerth, Manager, Advertising and Labeling
Harji Patel, Ph.D., Associate Director, Biostatistics
Marie Foegh, M.D., Medical Director
Kelly Parsey, M.D., Senior Associate Medical Director
Kishor Dandekar, Ph.D., Associate Director, Clinical Pharmacology
Adel Karara, Ph.D., Associate Director, Clinical Pharmacology
Don Atkinson, Director, Marketing
Jeff Frick, Strategic Business Director
Nancy Bauer, Research Toxicologist

Meeting Objective: To discuss the status of the pending action as of this time; 2-month PDUFA goal date is today, July 10, 2000.

Background:
Yasmin is a combination oral contraceptive and contains a new molecular entity, drospirenone (DRSP), a progestin that has anti-mineralocorticoid activity similar to that of spironolactone. There has been much discussion at the Division, Office and Center levels regarding the Action to be taken on this product due to a reanalysis of the risk/benefit profile.

Discussion:
- recommended action at this time is Approvable (AE); a reanalysis of the risk/benefit profile has demonstrated the need for additional studies to assess and understand the risk of hyperkalemia in women using Yasmin, and to assure safety among users of the product
- the Sponsor expected an Approval action and felt that their agreement to the Phase 4 commitment proposals addressed the potential safety issues; the Phase 4 commitments will be contained in the Approvable letter, but are subject to change based on new study data
- per Dr. Houn, the Center policy is highly focused on risk management issues and obtaining an accurate and robust assessment of risk in the pre-approval phase when possible
- at this time the Division does not have specific recommendations for clinical study designs on assessing hyperkalemia risk that would provide the most valuable information without additional research, discussion, or consultation with the Cardio-Renal Division; some examples of additional studies might include: additional studies in renally and hepatically impaired patients, drug:drug interaction studies, studies to demonstrate the therapeutic range of safety of DRSP, assessing spironolactone data to support that long term use of DRSP is safe; and more studies in the HRT population to show that product is well tolerated in an older population; studies in which the dose and the population at risk are pushed
- the HRT application present greater potential safety concerns and additional studies would be helpful for both applications
- additional information to support a unique benefit of Yasmin over other oral contraceptives would lend additional information to the risk/benefit assessment for Yasmin

Decisions:
- sponsor should compile a meeting package with available supportive data as suggested , and proposed additional studies to assess hyperkalemia risk with rationale in order to add to known safety database
- sponsor should propose a meeting to address the issues put forth today and in the Approvable letter

Action items:
- Action letter reflecting the Office decision regarding approval to be sent by COB July 10, 2000
- sponsor to request a Type A meeting and provide meeting package two weeks prior to the scheduled meeting
- Meeting Minutes to the sponsor within 30 days

/S/

Minutes Preparer

/S/

Concurrence, Chair

Note to Sponsor:
These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

cc:
Original NDA
HFD-580/DivFile
HFD-580/Best
HFD-580/Allen/Mann/Monroe/Shames/Rumble
HFD-103/Houn
drafted:JAB/July 10, 2000/
concurrence:Monroe,07.10.00/Rumble,07.10.00/Shames,07.11.00/Mann,07.11.00/Allen,07.11.00
final:JAB/July 12,2000

MEETING MINUTES

Teleconference Meeting Minutes

Date: July 5, 2000 **Time:** 4:10-4:50 pm **Location:** Parklawn; 17-B45

NDA 21-098 **Drug:** Yasmin® 28 Tablets (drospirenone and ethinyl estradiol)

Indication: Oral Contraception

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Action Status/Labeling/Phase 4 Commitments

Meeting Chair: Dr. Marianne Mann

External Lead: Ms. Nancy Velez

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Florence Houn, M.D., M.P.H., Office Director, Office of Drug Evaluation III (ODE III; HFD-103)
Susan Allen, M.D., M.P.H., Director, Division of Reproductive and Urologic Drug Products, (DRUDP; HFD-580)
Marianne Mann, M.D., Deputy Director, DRUDP (HFD-580)
Dan Shames, M.D., Team Leader, DRUDP (HFD-580)
Scott Monroe, M.D., Medical Officer, DRUDP (HFD-580)
Evelyn Rodriguez, M.D., Director, Division of Drug Risk Evaluation II (DDRE II; HFD-440)
Kathleen Uhl, M.D., Deputy Director, DDRE II (HFD-440)
Denise Toyer, Pharm.D., Safety Evaluator, DDRE II (HFD-440)
Kim Colangelo, B.S., Acting Chief, Project Management Staff
Jeanine Best, M.S.N., R.N., Regulatory Project Manger, DRUDP (HFD-580)

External Attendees:
Berlex Laboratories, Inc.
Nancy Velez, Manager, Drug Regulatory Affairs
Sharon Brown, Associate Director, Regulatory Affairs
Nancy Konnerth, Manager, Advertising and Labeling
Harji Patel, Ph.D., Associate Director, Biostatistics
Marie Foegh, M.D., Medical Director
Kelly Parsey, M.D., Senior Associate Medical Director
Kishor Dandekar, Ph.D., Associate Director, Clinical Pharmacology
Adel Karara, Ph.D., Associate Director, Clinical Pharmacology
Don Atkinson, Director, Marketing
Jeff Frick, Strategic Business Director
Louis Mylecraine, Ph.D., DABT, Associate Director, Preclinical Development

Meeting Objective: To discuss the status of the pending Action, provide labeling comments, and discuss Phase 4 commitment proposals.

Background:

- There is a real emphasis in the Agency now to address risk management issues pre-approval whenever possible; we have two signals of concern for Yasmin: potential for hyperkalemia, and possible fetal toxicity (due to a single case of esophageal atresia); addressing these potential risks more thoroughly pre-approval has been considered and discussed at the Office level and above, particularly since Yasmin poses no known benefits over other approved oral contraceptives; to be very explicit, a non-approval action of this NDA has been considered and discussed.
- Additional concerns shared by both the Division and the Office include the fact that this application includes reliable Phase 3 serum potassium data from only a single pivotal trial (the U.S. study) whereas all other long-term controlled safety data is unreliable due to mishandling (hemolyzed specimens) of blood samples; in addition, while there is some data on renally impaired subjects, this is limited to 17 subjects.
- The Division has also discussed the above concerns with the Office; together, we have derived some revised labeling, as well as phase 4 studies that may support an approval action; the purpose of this teleconference is to share these specific labeling issues and Phase 4 study plans with the sponsor; conversations are still underway regarding aprovability, however.

Discussion:

- Labeling: Two labeling changes of significance were discussed:
  Page 2 of the labeling most recently provided by the sponsor, under **PHARMACODYNAMICS**:
  Combine 2nd and 3rd paragraphs in this section and revise them to read:

  "Drospirenone is a spironolactone analogue with antimineralocorticoid activity. Preclinical studies in animals and *in vitro* have shown that drospirenone has no androgenic, estrogenic, glucocorticoid, and antiglucocorticoid activity. Preclinical studies in animals have also shown that drospirenone has antiandrogenic activity."

  Page 6 of the labeling, the **BOLDED WARNING** has been rewritten to read:

  "Yasmin is contraindicated in patients with renal insufficiency, hepatic dysfunction, or conditions that predispose to hyperkalemia. Yasmin contains 3 mg of the progestin dropsirenone, which has antimineralocorticoid activity comparable to a 25 mg dose of spironolactone. Potential risks of Yasmin include hyperkalemia, hyponatremia, and metabolic acidosis."

- The Patient Package Insert should likewise have the **BOLDED WARNING** rewritten to read:

  "Yasmin should not be taken by women who have kidney or liver disease, or who have conditions that can lead to high blood potassium levels. Possible risks of Yasmin include increases in blood potassium levels and decreases in blood sodium levels.

- Sponsor was asked to confirm the accuracy of the statement: "Yasmin contains 3 mg of the progestin dropsirenone, which has antimineralocorticoid activity *in vitro* comparable to a 25 mg dose of spironolactone." Sponsor was also asked to address if this was demonstrated *in vitro* or *in vivo* (or both).
- Additional minor labeling edits will also be faxed to the sponsor by close of business (COB) today.

- Phase 4 studies desired by the Division were then discussed; sponsor should commit to providing a full program/protocol to address these phase 4 commitments within 120 days of approval. Commitment to in writing is required prior to approval. Submit the protocols for these studies in 120 days.

- The first Phase 4 commitment was for the sponsor to provide an educational outreach program for health care providers and patients, focusing on Yasmin's contraindications in patients with renal/hepatic impairment or patients predisposed to hyperkalemia due to its potential antimineralocorticoid activity
- The second Phase 4 commitment was a surveillance or evaluation program to evaluate the inappropriate prescribing of Yasmin to patients with underlying hepatic or renal dysfunction using a database of Yasmin users; the database would provide a list of all Yasmin users, and these patients would then be screened carefully for any past or recent diagnoses of hepatic and/or renal dysfunction; full case report summaries of all such inappropriate prescriptions, including patient outcome, would then be required.
- The third Phase 4 commitment would be to use the same (or different) database to again evaluate all patients prescribed Yasmin for the subsequent outcome of death, hospitalization, syncope, arrhythmia, hyperkalemia, electrolyte disturbances, dialysis, etc (other search terms may also be considered appropriate); patients taking Yasmin and experiencing these types of events (or taking Yasmin within one month of such events) would be considered concerning; full case reports summaries, including patient outcome, would be required for these patients.
- The sponsor should provide a sample size calculation, which would be adequate to detect inappropriate prescribing in the patient population.
- The fourth Phase 4 commitment would be to analyze more carefully pregnancy outcomes which occur in patients exposed to Yasmin; this could be done in the same cohort of Yasmin users described in the database; in addition, the Organization of Teratogen Information Services (OTIS), or other resources could be used to collect data on all patients reporting a Yasmin exposure; a pregnancy exposure registry is an alternative; outcome on as many patients as possible is desired and may require several years of follow-up; finally, collecting all post-marketing adverse event reports and placing them in a format to help identify signals of developmental toxicity is recommended.
- The sponsor may refer to the Draft Guidance, "Establishing Pregnancy Registries".
- The Agency would expect updates on these Phase 4 activities, including reports, quarterly.

Additional Items for Discussion:

- The Division feels that a single case of serious or life threatening hyperkalemia that appears related to Yasmin use or a single additional major congenital anomaly (particularly one related to branchial pouch development such as esophageal atresia) reported post-marketing in association with Yasmin use would pose concern that might lead to an Agency decision to withdraw Yasmin.
- The Division feels that cases of hyperkalemia that are not serious/life-threatening, or do not appear related to Yasmin use would nonetheless pose concerns significant enough to consider product withdrawal, or possibly an Advisory Panel meeting, or restricted use, or a black-box warning with a Dear Health Care Practitioner letter possibly; additional reports of major congenital anomalies would be considered with similar possible outcomes.
- The Division advised the sponsor to perform additional studies that might prove unique benefits of Yasmin over other approved oral contraceptives; therefore, supporting it's particular risk profile with demonstrated clinical benefits over existing oral contraceptive alternatives.

- The Division addressed the sponsor's upcoming pre-NDA meeting for their drospirenone based (Hormone Replacement Therapy) HRT product (also containing 3 mg of drospirenone); a Cardio-Renal consult of this package will be requested; in addition, if the sponsor wishes to update their package for this meeting with respect to how hyperkalemia risk and metabolic acidosis will be specifically addressed: information that would be useful would include a summary of how many patients were followed and what type of serum potassium data will be available, a summary of all Serious Adverse Events (SAEs) reported in the database to date, a summary of all drug:drug interaction studies that will be performed to address potential risks for hyperkalemia, etc. The sponsor should submit such a summary within one week of submission of their meeting package.

Decisions:

- The Division, with OPDRA input, is committed to a rapid turnover for review and comments of sponsor's submitted Phase 4 protocols.

Action items:

- J. Best to send labeling comments and Phase 4 commitment proposals electronically by COB today
- Sponsor to submit labeling and agreement to Phase 4 commitment proposals by 12 noon, July 7, 2000
- Action letter reflecting the Office decision regarding approval to be sent by COB July 10, 2000
- Meeting Minutes to the sponsor within 30 days

/S/

Minutes Preparer

/S/

Concurrence, Chair

7/10/00

Note to Sponsor:

These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA
HFD-580/DivFile
HFD-580/Best
HFD-580/Allen/Mann/Monroe/Shames/Colangelo
HFD-103/Houn
HFD-440/Rodriguez/Uhl/Toyer
drafted:JAB/July 5, 2000
concurrence:Houn,07.05.00/Shames,07.06.00/Colangelo,07.06.00/Toyer,07.06.00/Monroe,07.06.00/Mann,07.06.00/Uhl,07.06.00/Rodriguez,07.06.00/Allen,07.10.00
final:JAB/July 10, 2000

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

Teleconference Meeting Minutes

Date: June 21, 2000 **Time:** 3:00-3:10 pm **Location:** Parklawn; 17-B45

NDA 21-098 **Drug:** Yasmin® 28 Tablets (drospirenone and ethinyl estradiol)
Tablets\

Indication: Oral Contraception

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Labeling Revision

Meeting Chair: Dr. Marianne Mann

External Lead: Ms. Nancy Velez

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
Jeanine Best, M.S.N., R.N., Regulatory Project Manger, DRUDP (HFD-580)

External Attendees:
Nancy Velez, Manager, Drug Regulatory Affairs, Berlex Laboratories, Inc.

Meeting Objective: To convey additional label edit to the sponsor.

Background: On May 9, 2000, the sponsor submitted a complete response to the approvable action of March 17, 2000, for their drospirenone/ethinyl estradiol product. Drospirenone (DRSP) is a new progestin and differs from other progestins in that it has antimineralocorticoid activity.

Discussion:

- sponsor was asked to revise the following statement in the **Interactions With Drugs That Have The Potential To Increase Serum Potassium** subsection to read:

  Serum potassium concentrations were measured at multiple timepoints over 24 hours at baseline and on Day 14. On Day 14, DRSP/E2 and placebo groups had mean serum AUC potassium values within XX-XX% of each other, and mean serum Cmax potassium values within XX-XX% of each other."

- the term "bioequivalence" has a specific meaning in the Agency, namely, the comparison of serum drug levels between drugs; it is never used to describe serum potassium levels, and the the limits of 80-125% may not apply to potassium; these limits may not be clinically relevant

- for future potassium assessments look at mean changes from baseline and the number of patients that exceed the upper limit of normal; comparisons of 24 hour AUC and Cmax serum potassium values are not considered necessary or relevant

Action Items:

- J. Best to fax Physician label revision by COB today
- Berlex to return revised Physician label (paper copy) by Friday morning, June 23, 2000

/S/

Minutes Preparer

/S/

Concurrence, Chair

6/21/00

Note to Sponsor:
These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

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cc:
Original NDA
HFD-580/DivFile
HFD-580/Best
HFD-580/Mann

drafted:JAB/June 21, 2000
concurrence:
final:

MEETING MINUTES