[redacted] has been omitted. This is acceptable, given that the information largely described negative findings and that the cardiovascular effects of salmeterol are described in the PRECAUTIONS section. Pharmacodynamics for fluticasone are adapted from the Flovent labels. Verbage regarding fluticasone's [redacted] has been omitted, but this information is contained to a limited extent in the Pharmacokinetics subsection. Pharmacodynamics for Advair are described by ingredient.

CLINICAL TRIALS:
- Pivotal Trials SFCA3002, SFCA3003 and SFCB 3019 are extensively described, as are each of the supportive trials. As proposed, there are 250 lines of text, — plots and ~ tables. Recommendations for shortening this section will be provided in a comment to the sponsor.
- The AQLQ global scores are included as secondary endpoints. Based on consultation with DDMAC, the sponsor should be advised that a final decision regarding use of QOL endpoints in labeling and marketing materials is pending.

INDICATIONS AND USAGE:
- The sponsor as proposed the indication [redacted] As discussed with the PADAC on November 23, 1999, this indication does not provide prescribers with an adequate appreciation of the population studied or the patients in whom this product is expected to achieve efficacy. The sponsor will be asked to revise their proposal.

CONTRAINDICATIONS:
- This section is adequate.

WARNINGS:
- This section provides the box warning for corticosteroids (withdrawal of oral corticosteroids / adrenal supression), but does not include specific wording on weaning from oral corticosteroids.
- The box warning should clarify that the product should not be used for an indication of oral corticosteroid sparing and patients who are currently using oral corticosteroids should not be switched directly to Advair.
- Warnings are included regarding unmasking of other conditions with decreased doses and use in immunosuppression. A section has been added advising against use with other long-acting beta$_2$-agonists. Approved language for salmeterol formulation warnings is included with slight modifications. The subsequent labeling proposal should be reviewed for a final determination of text in this section.

PRECAUTIONS:
- "General," "Metabolic and Other Effects," "Eosinophilic Conditions," "Information for Patients," and sections on carcinogenesis, pregnancy, labor and delivery, and nursing are derived from Serevent and Flovent labeling with minor wording changes.

- Drug interactions are derived from the Advair clinical trials, as well as Serevent and Flovent labeling and include short acting $beta_2$ agonists, methylxanthines, fluticasone nasal spray, MAOI's, TCA's, beta-blockers, diuretics and inhibitors of cytochrome P450.
- The pediatrics section generally describes Trial SFCB3020. In addition, a statement regarding potential growth suppression is made. The latter should be made consistent with the approved labeling for other Flovent formulations at the time of approval.
- Based on available data, no recommendation for dose adjustment is made for geriatric patients.

ADVERSE REACTIONS:
- This section is based on Trials SFCA3002, SFCA3003 and SFCB3019. Since this differs from the ISS (which was based on five studies), the sponsor should be asked for source documentation.

OVERDOSAGE:
- This section contains information from Serevent and Flovent labeling, as well as Advair trials. It should be established by the pharmacologist that the calculations are appropriate for the Advair formulation. Also, this section could be better integrated, with Advair information followed by that of the individual ingredients. Final wording can be created upon review of the subsequent draft.

DOSAGE AND ADMINISTRATION:
- [redacted] currently proposed, entitled "[redacted] It is unclear that these [redacted] are consistent with the current INDICATIONS section, but should be related in final labeling.
- [redacted]
- [redacted]

HOW SUPPLIED:
- This section appears to be acceptable, but requires further review from the chemist.

The "Patient's Instruction for Use" section was compared to the currently approved version for Serevent Diskus. The following changes are noted:

- This section has been significantly reformatted with improved subsection headings for ease of use.
- A general statement regarding pharmacology and indication has been added.

- Dose frequency should not be decreased without physician instructions and doses should not be doubled. Patients are instructed to advise physician if symptoms are not improved within two weeks.
- As compared to the Serevent labeling, the Advair labeling contains less specificity with regard to instructions for seeking medical attention for increased use of concurrent short-acting beta agonists. The general statements regarding caution about increasing number or frequency of doses is adequate.
- The labeling states that the product should not be used with Serevent Diskus or Inhalation Aerosol.
- Instructions for operation of the device nearly identical to that of the Serevent Diskus. Minor wording changes enhance clarity.
- Comments have been received from Karen Lechter in DDMAG and should be encorporated appropriately into the final labeling.

In addition, the following items should be verified in the final version of the labeling.

- The approvable tradename has been used consistently.
- Instructions for "use by" date in the labeling and patient instructions is the approvable date.
- Additional comments are expected from OPDRA regarding the medications errors review. These should be encorporated, as appropriate.

The following comments should be forwarded to the sponsor regarding the proposed labeling.

At this time, we are providing the following general comments regarding the labeling proposed in your January 13, 2000 submission. Additional comments can be expected pending our review of the subsequent draft.

1. The proposed tradenames, "Advair Diskus ———' Advair Diskus———" and "Advair Diskus ———," are not acceptable, although the prefix Advair is allowable. Select tradenames that clearly reflect that both salmeterol and fluticasone are contained in the product.

2. The CLINICAL TRIALS section should be considerably shortened. Outcomes of Trial ——— can be described in reference to outcomes of Trial ———:, as can secondary endpoints for Trial ——— Verbal descriptions are adequate for onset of action and progression of improvement in these trials. ——— A final determination of the appropriate use of quality of life data in labeling and marketing materials is pending.

3. Per our review and the November 23, 1999 discussion of the Pulmonary Allergy Drugs Advisory Committee, revise the proposed indication for "patients 12 years of age and older——— to better reflect the

population studied and delineate the population expected to benefit from Advair therapy.

4. The box warning should clarify that these products should not be used for [redacted] indication and that patients who are currently using oral corticosteroids should not be switched directly to Advair.

5. Provide references to the source documentation from the original NDA (volume and pages numbers) for the summary data contained in the ADVERSE REACTIONS section.

6. Remove Table [redacted] from the DOSAGE AND ADMINISTRATION section.

XIII. APPENDICES

[redacted]

APPEARS THIS WAY
ON ORIGINAL

APPENDIX A

1. Principal Investigators for Trial SFCA3002 - Each investigator is an M.D. The number of patients enrolled by each investigator is indicated in parentheses.

Thomas D. Bell, Missoula MT (17)
B. Lauren Charous, Milwaukee WI (0)
Paul Chervinsky, North Dartmouth, MA (31)
Robert Cohen, Lawrenceville GA (21)
John Condemi, Rochester NY (4)
Gerald Davis, Burlington VT (2)
Thomas Edwards, Albany NY (21)
David Elkayam, Bellington WA (3)
Stanley Galant, Orange GA (5)
David Graft, Minneapolis MN (11)
Gary Gross, Dallas TX (19)
Alan Heller, San Jose CA (0)
Gary Incaudo, Chico CA (4)
John Jeppson, Boise ID (4)
Harold Kaiser, Minneapolis MN (11)
Mani Kavuru, Cleveland OH (11)
William Kinnard, Boulder CO (4)
Philip Korenblat, St. Louis MO (0)
Craig LaForce, Raleigh NC (17)
Ed Lisberg, Oak Park IL (5)
Julian Melamed, Chelmsford MA (10)
Don Mitchell, Jackson MS (16)
Federico Montealegre, Ponce PR (10)
Melvin Morganroth, Portland OR (6)
Zev Munk, Houston TX (0)
Robert Nathan, Colorado Springs CO (11)
Anjuli Nayak, Normal IL (2)
Robert Noveck, New Orleans LA (1)
David Pearlman, Aurora CO (12)
Andrew Pedinoff, Princeton NJ (8)
Gordon Raphael, Bethesda MD (10)
Brian Schwartz, Baltimore MD (1)
Nathan Segall, Atlanta GA (0)
Gail Shapiro, Seattle WA (7)
G. Edward Stewart II, Ocala FL (5)
James Taylor, Tacoma WA (14)
Allan Weinstein, Washington DC (3)
Steven Weinstein, Huntington Beach CA (27)
Martha V. White, Washington DC (0)
John Winder, Sylvania OH (0)
Hugh Windom, Sarasota FL (5)
James Wolfe, San Jose (18)

2. Principal Investigators for Trial SFCA3003 - Each investigator is an M.D. The number of patients enrolled by each investigator is indicated in parentheses.

James Baker, Portland OR (14)
George Bensch, Stockton CA (3)
Edwin Bronsky, Salt Lake City UT (0)
Paul Chervinsky, North Dartmouth, MA (21)
Bradley Chipps, Sacramento CA (1)
Karen Dunn, Raleigh NC (10)
Thomas Edwards, Albany NY (12)
Linda Ford, Papillon NE (2)
John Given, Canton OH (4)
Jay Grossman, Tuscon AZ (4)
Robert Grubbe, Anniston AL (3)
Melvin Haysman, Savannah GA (6)
Mary Brandt Hudelson, Flower Mound TX (4)
Bob Lanier, Ft. Worth TX (1)
Michael Lawrence, Taunton MA (13)
Ted Lee, Atlanta GA (6)
Ed Lisberg, Oak Park IL (5)
William Lumry, Dallas TX (14)
Louis Mendelson, West Hartford CT (12)
Federico Montealegre, Ponce PR (5)
Zev Munk, Houston TX (12)
Anjuli Nayak, Normal IL (14)
David Pearlman, Aurora CO (11)
Andrew Pedinoff, Princeton NJ (14)
Jacob Pinnas, Tucson AZ (19)
Warren Pleskow, Encinitas CA (10)
Brian Schwartz, Baltimore MD (0)
Nathan Segall, Atlanta GA (3)
John Selner, Denver CO (9)
Guy Settipane, Providence RI (1)
Gail Shapiro, Seattle WA (14)
William Sokol, Newport Beach CA (4)
James Taylor, Tacoma WA (17)
Dwayne Thomas, New Orleans LA (5)
Timothy Tolson, Elizabeth City NC (5)
Mark Vandewalker, Jefferson City MO (11)
Michael Volz, Denver CO (0)
Steven Weinstein, Huntington Beach CA (12)
Martha V. White, Washington DC (11)
John Winder, Sylvania OH (0)
Hugh Windom, Sarasota FL (19)
James Wolfe, San Jose CA (9)
Robert N. Wolfe, Los Angeles CA (9)

APPENDIX B

AQLQ and Sleep Scale

APPEARS THIS WAY
ON ORIGINAL

Protocol Code	Session	Subject No
SFCA3002	2	

VISIT 2

Part A*: Asthma Specific Questions

Date completed: Month / Day / Year

Below are questions about your health as it relates to asthma.

Activities: Please think of ways in which asthma places limitations on your life and activities. We are particularly interested in activities that you still do, but which are limited by your asthma. You may be limited because you do these activities less often, or less well, or because they are less enjoyable. These should be activities which you do frequently and which are important in your day-to-day life. These should also be activities that you intend to do regularly throughout the study.

Please think of all the activities which you have done during the last 2 weeks, in which you were limited as a result of your asthma.

Here is a list of activities in which some people with asthma are limited. We hope that this will help you to identify the 5 most important activities in which you have been limited by your asthma during the last 2 weeks.

1.	Bicycling	15.	Shovelling snow
2.	Cleaning snow off your car	16.	Singing
3.	Dancing	17.	Doing regular social activities
4.	Doing home maintenance	18.	Having sexual intercourse
5.	Doing your housework	19.	Sleeping
6.	Gardening	20.	Talking
7.	Hurrying	21.	Running upstairs or uphill
8.	Jogging or exercising or running	22.	Vacuuming
9.	Laughing	23.	Visiting friends or relatives
10.	Mopping or scrubbing the floor	24.	Going for a walk
11.	Mowing the lawn	25.	Walking upstairs or uphill
12.	Playing with pets	26.	Woodwork or carpentry
13.	Playing with children or grandchildren	27.	Carrying out your activities at work
14.	Playing sports	28.	Other

Please write your 5 most important activities on the following page.

Protocol Code	Session	Subject No
SFCA3002	2	

VISIT 2

Please write your 5 most important activities on the lines below and then tell us how much you have been limited by your asthma in each activity during the last 2 weeks by checking the box with the appropriate rating.

How limited have you been during the last 2 weeks in these activities?

Activities	Totally Limited 1	Extremely Limited 2	Very Limited 3	Moderate Limitation 4	Some Limitation 5	A Little Limitation 6	Not at all Limited 7
1.							
2.							
3.							
4.							
5.							

How much discomfort or distress have you felt over the last 2 weeks?

	A Very Great Deal 1	A Great Deal 2	A Good Deal 3	Moderate Amount 4	Some 5	Very Little 6	None 7
6. How much discomfort or distress have you felt over the last 2 weeks as a result of chest tightness?							

In general, how much of the time during the last 2 weeks did you:

	All of the Time 1	Most of the Time 2	A Good Bit of the Time 3	Some of the Time 4	A Little of the Time 5	Hardly Any of the Time 6	None of the Time 7
7. Feel concerned about having asthma?							
8. Feel short of breath as a result of your asthma?							
9. Experience asthma symptoms as a result of being exposed to cigarette smoke?							
10. Experience a wheeze in your chest?							
11. Feel you had to avoid a situation or environment due to cigarette smoke?							

Protocol Code	Session	Subject No
SFCA3002	2	

VISIT 2

How much discomfort or distress have you felt over the **last 2 weeks?**

	A Very Great Deal 1	A Great Deal 2	A Good Deal 3	Moderate Amount 4	Some 5	Very Little 6	None 7
12. How much discomfort or distress have you felt over the last 2 weeks as a result of coughing?							

In general, how much of the time during the **last 2 weeks** did you:

	All of the Time 1	Most of the Time 2	A Good Bit of the Time 3	Some of the Time 4	A Little of the Time 5	Hardly Any of the Time 6	None of the Time 7
13. Feel frustrated as a result of your asthma?							
14. Experience a feeling of chest heaviness?							
15. Feel concerned about the need to use medication for your asthma?							
16. Feel the need to clear your throat?							
17. Experience asthma symptoms as a result of being exposed to dust?							
18. Experience difficulty breathing out as a result of your asthma?							
19. Feel you had to avoid a situation or environment because of dust?							
20. Wake up in the morning with asthma symptoms?							
21. Feel afraid of not having your asthma medication available?							
22. Feel bothered by heavy breathing?							
23. Experience asthma symptoms as result of the weather or air pollution outside?							
24. Were you awakened at night by your asthma?							

Protocol Code	Session	Subject No
SFCA3002	2	

VISIT 2

In general, how much of the time during the last 2 weeks did you:

	All of the Time 1	Most of the Time 2	A Good Bit of the Time 3	Some of the Time 4	A Little of the Time 5	Hardly Any of the Time 6	None of the Time 7
25. Avoid or limit going outside because of the weather or air pollution?							
26. Experience asthma symptoms as a result of being exposed to strong smells or perfume?							
27. Feel afraid of getting out of breath?							
28. Feel you had to avoid a situation or environment because of strong smells or perfume?							
29. Has your asthma interfered with getting a good night's sleep?							
30. Have a feeling of fighting for air?							

How limited have you been during the last 2 weeks?

	Most Not Done 1	2	Several Not Done 3	4	Very Few Not Done 5	6	No Limitation 7
31. Think of the overall range of activities that you would have liked to have done during the last 2 weeks. How much has your range of activities been limited by your asthma?							

	Totally Limited 1	Extremely Limited 2	Very Limited 3	Moderate Limitation 4	Some Limitation 5	A Little Limitation 6	Not at all Limited 7
32. Overall, among all the activities that you have done during the last 2 weeks, how limited have you been by your asthma?							

Protocol Code	Session	Subject No
SFCA3002	2	

VISIT 2

Part B: Sleep Scale

1. **During the past 4 weeks, how much sleep loss have you experienced because of your asthma symptoms?**

(circle one number)

None 1
Very mild 2
Mild 3
Moderate 4
Severe 5
Very severe 6

2. **During the past 4 weeks, how much did the lack of sleep, because of your asthma symptoms, interfere with your normal performance at work, housework or school ?**

(circle one number)

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

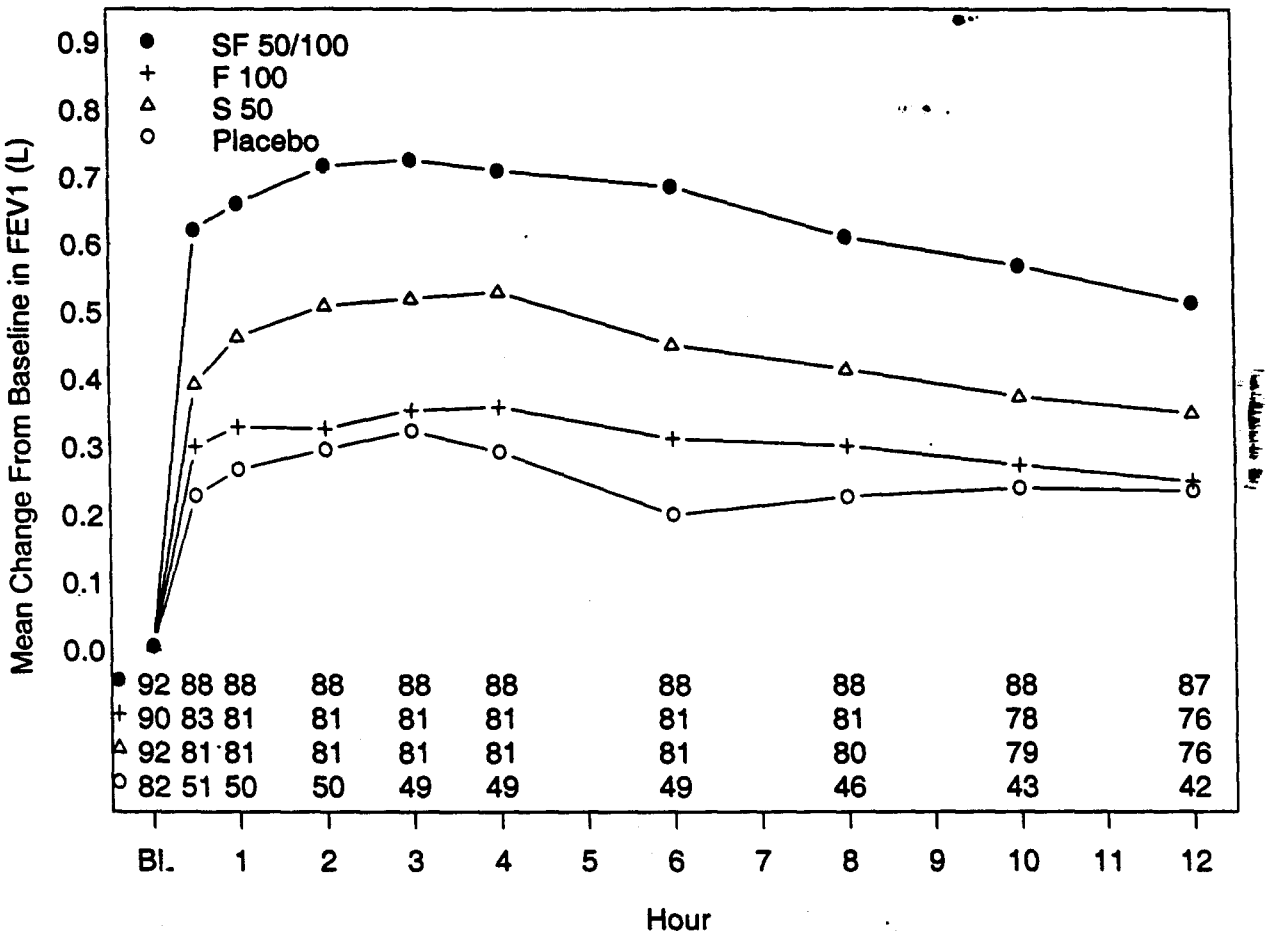
3. **During the past 4 weeks, how many nights have you awakened at least once because of your asthma symptoms?**

(circle one number)

None 1
Once 2
Less than 4 3
About once a week 4
More than once a week 5
Almost every night 6

APPENDIX C

Study SFCA3002: Hourly Mean Change from Baseline in FEV1 (n): Treatment Week 1



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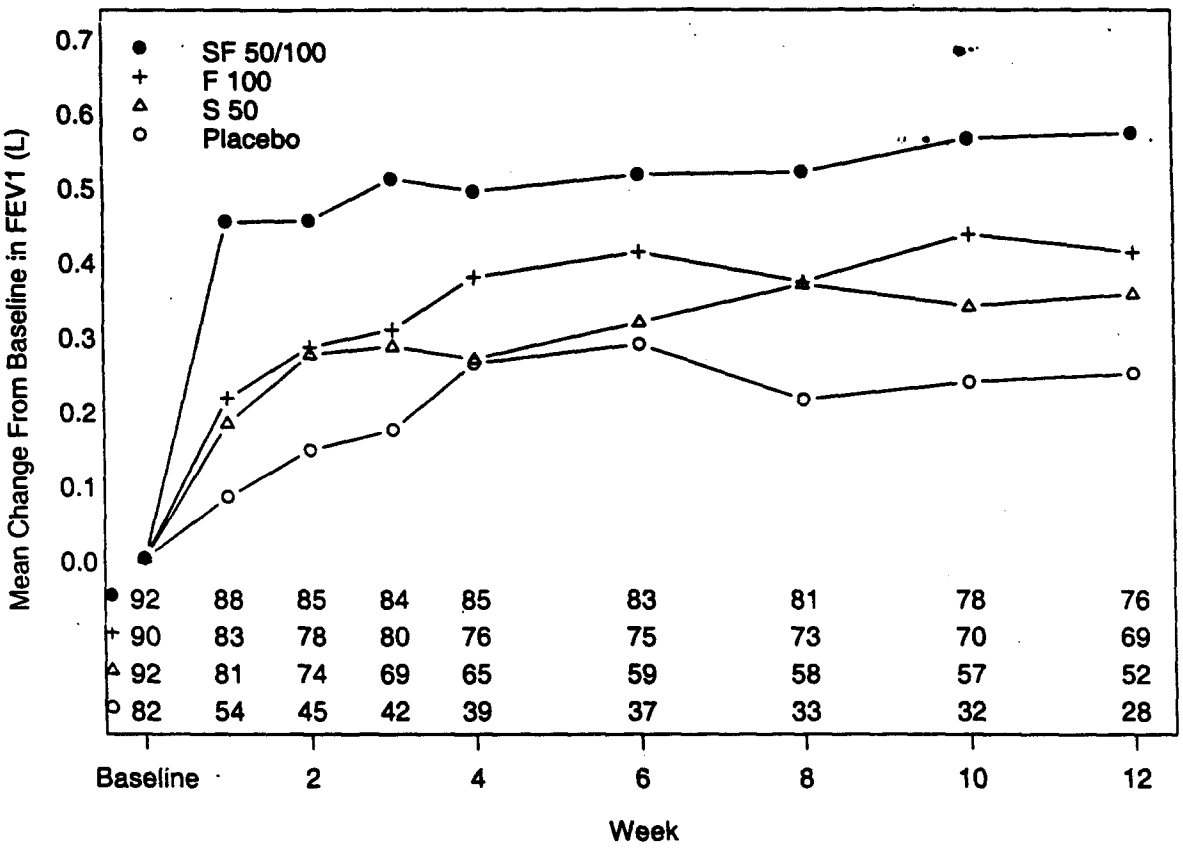
APPENDIX D

Study SFCA3002: Change from Baseline in Morning Predose FEV1 (n)



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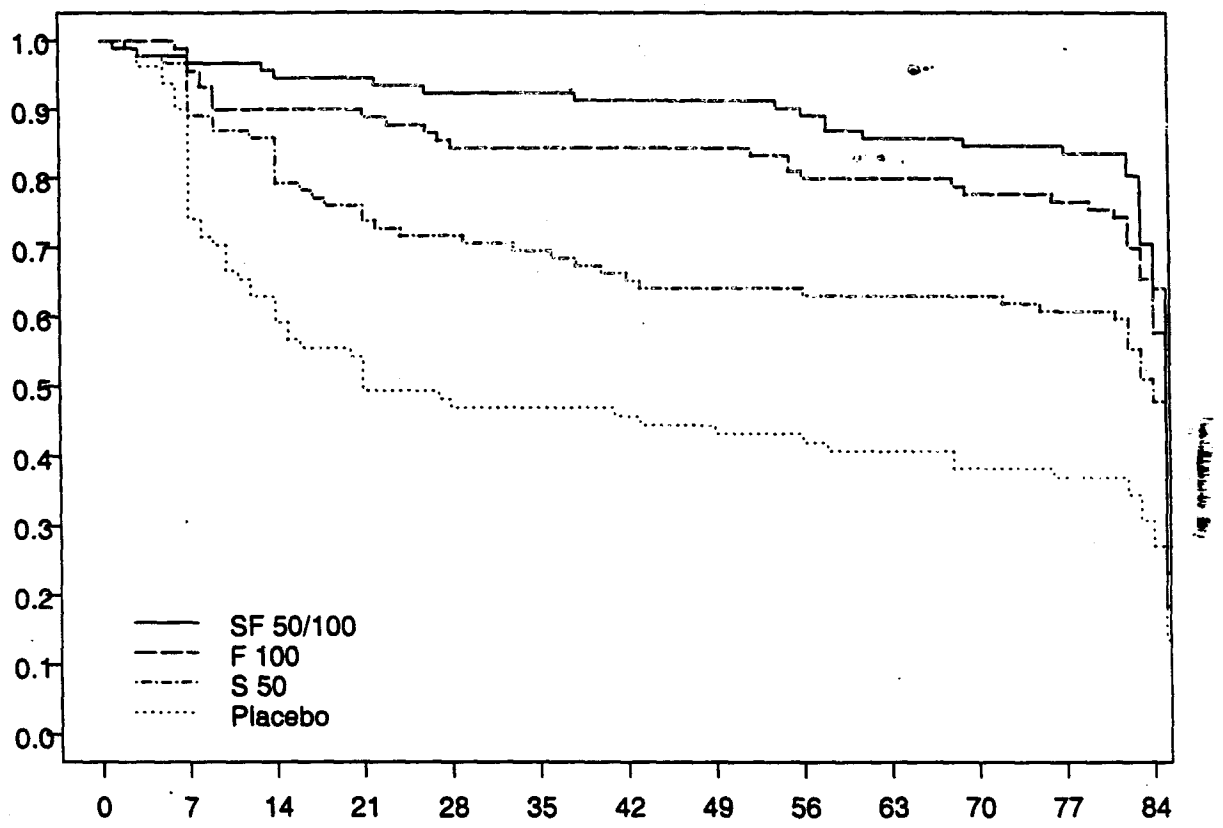
APPENDIX E

Study SFCA3002: Probability of Patients Remaining In the Study



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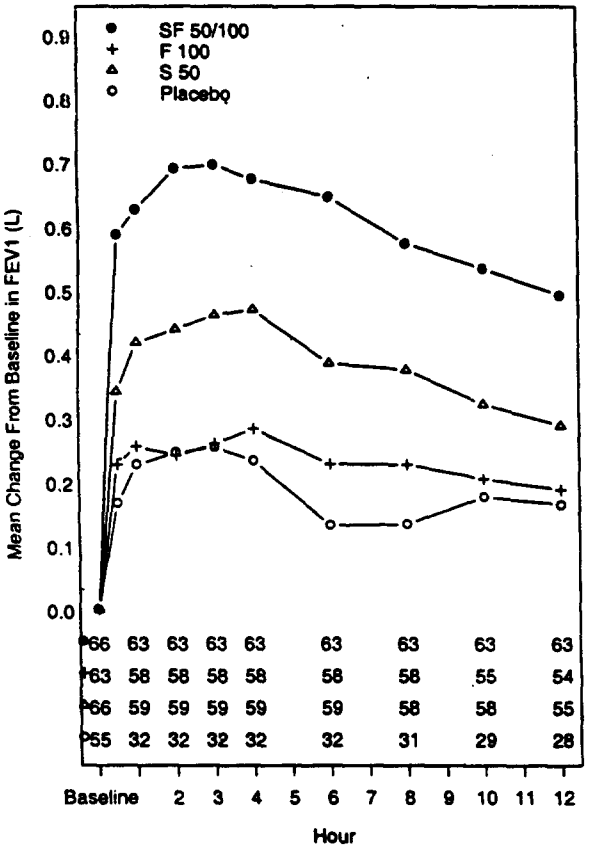
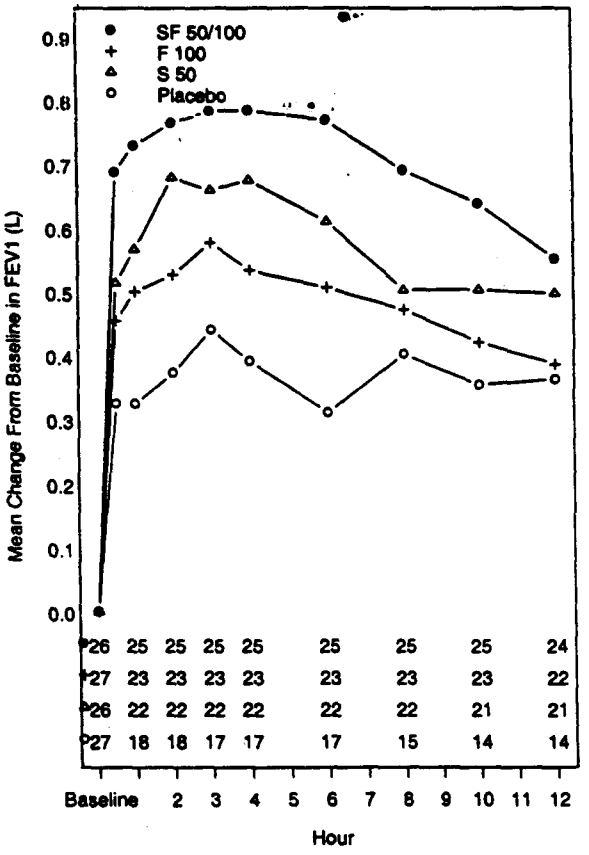
APPENDIX F

Study SFCA3002: Hourly Mean Change from Baseline in FEV1 (n): Treatment Week 1 by Pre-Study Medication Use Group

Prior Use: Inhaled Corticosteroids



Prior Use: Salmeterol



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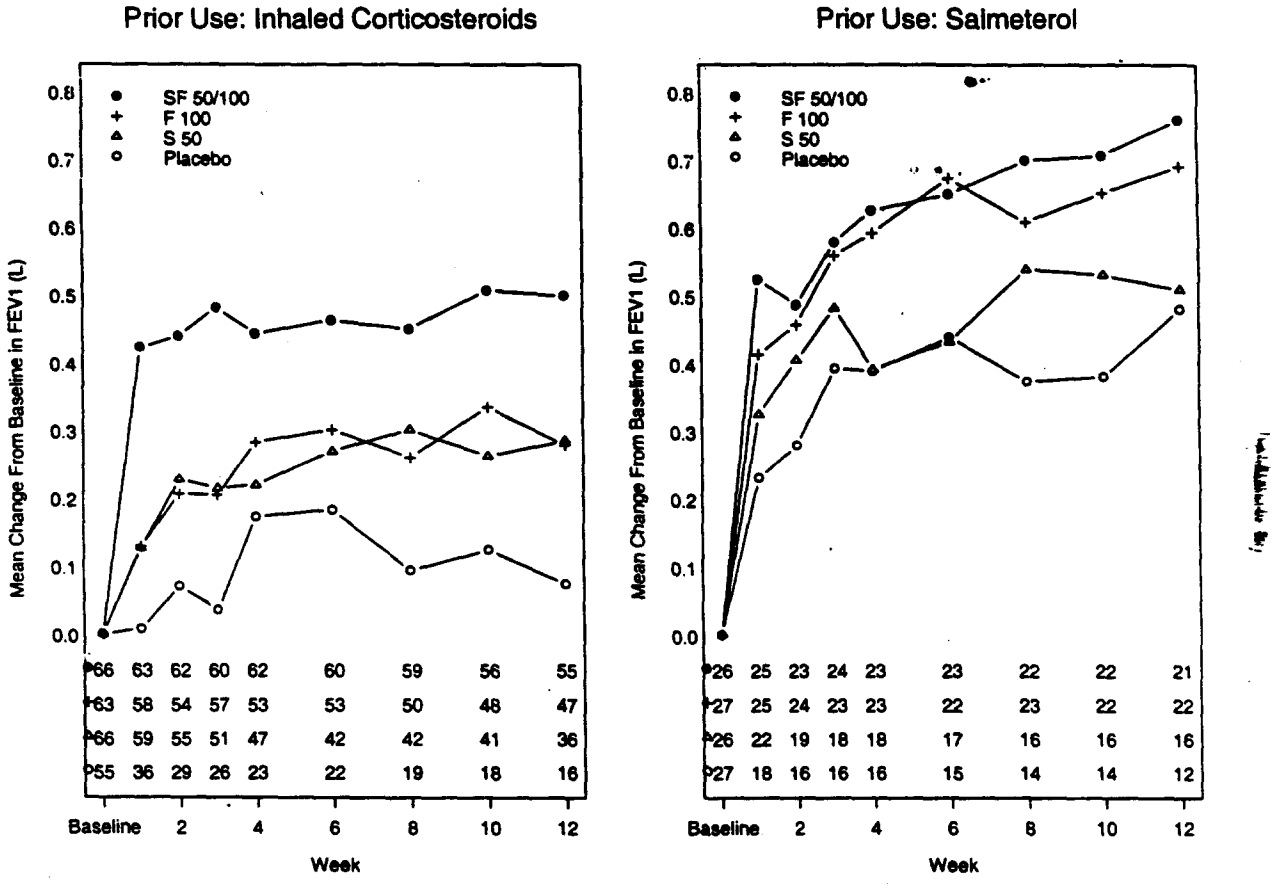
APPENDIX G

Study SFCA3002: Change from Baseline in Morning Predose FEV1 (n) by Pre-Study Medication Use Group



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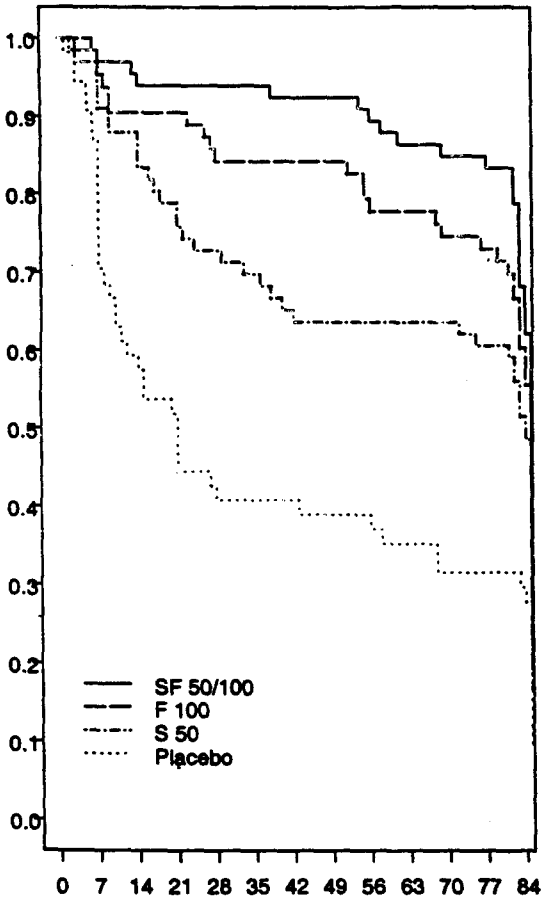
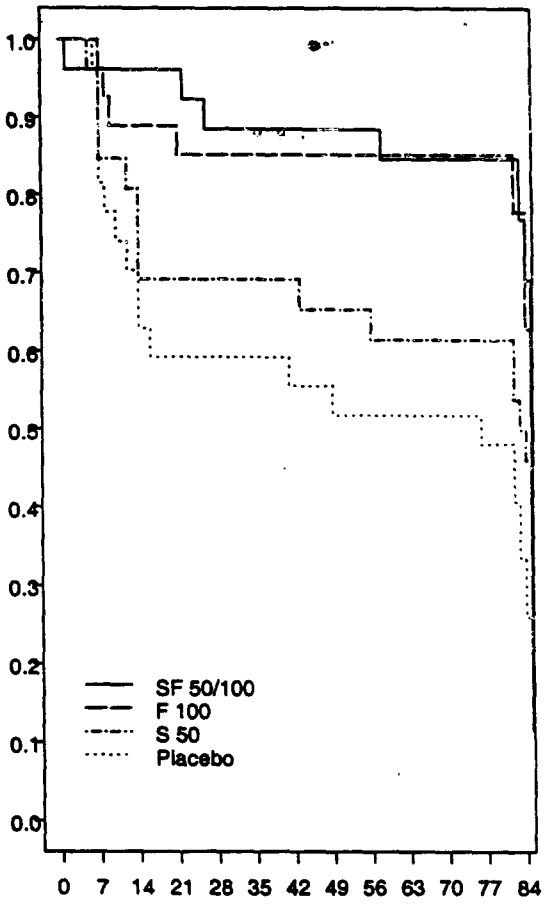
APPENDIX H

Study SFCA3002: Probability of Patients Remaining in Study by Pre-Study Medication Group

Prior Use: Inhaled Corticosteroids



Prior Use: Salmeterol



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APPENDIX I

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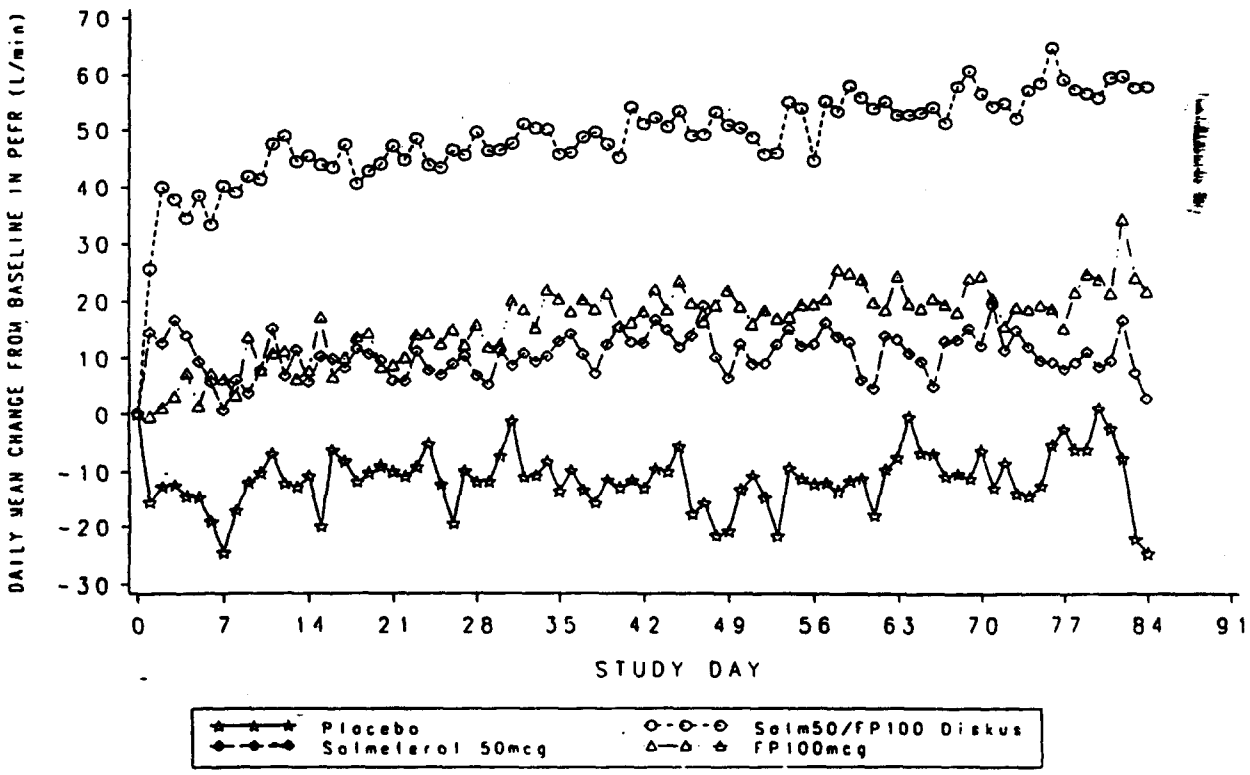
lmeterol/Fluticasone Propionate Diskus
>tocol: SFCA3002
>ulation: Intent-to-Treat

Change from Baseline in Morning Peak Expiratory Flow Rates -- Daily Means



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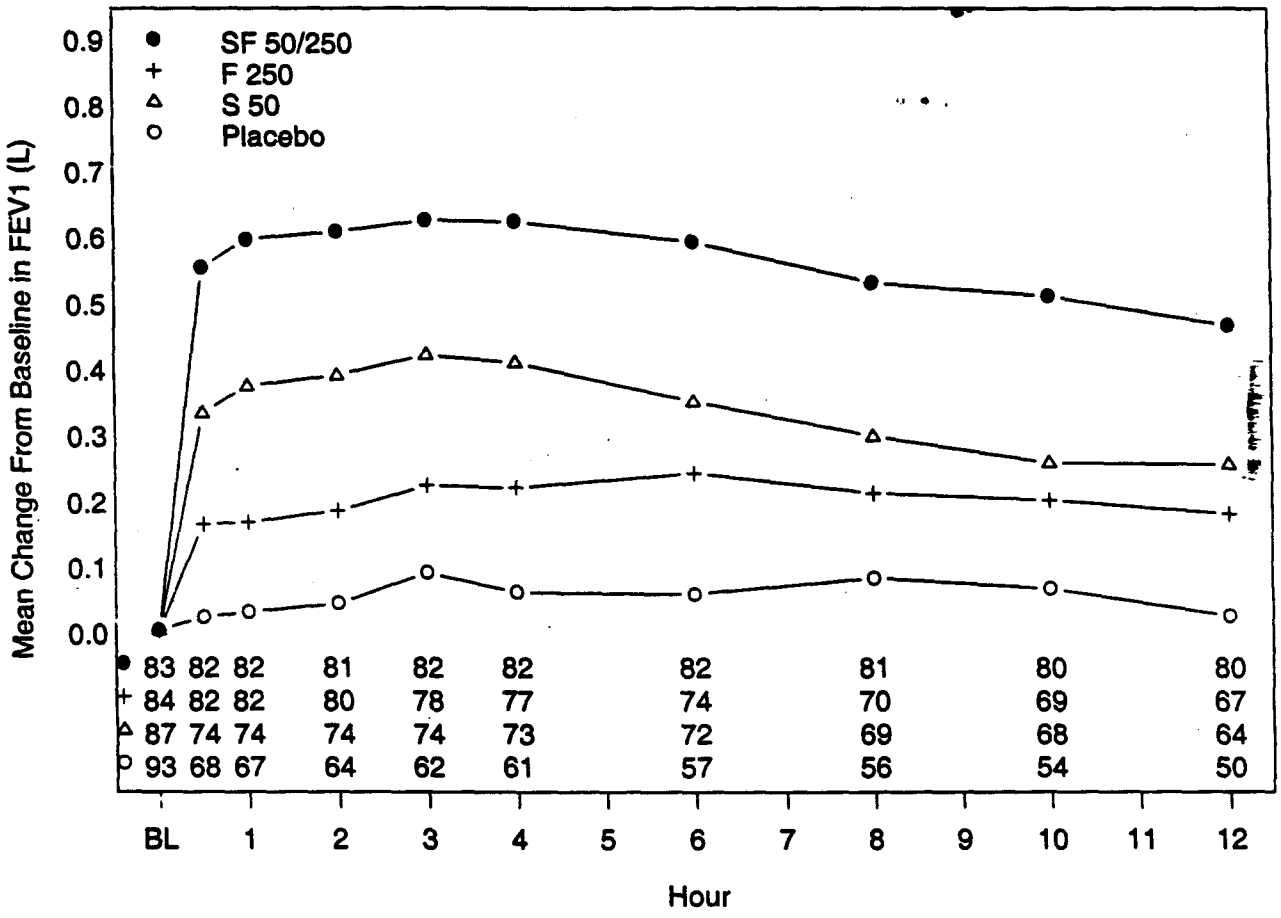
APPENDIX J

Study SFCA3003: Hourly Mean Change from Baseline in FEV1 (n): Treatment Week 1



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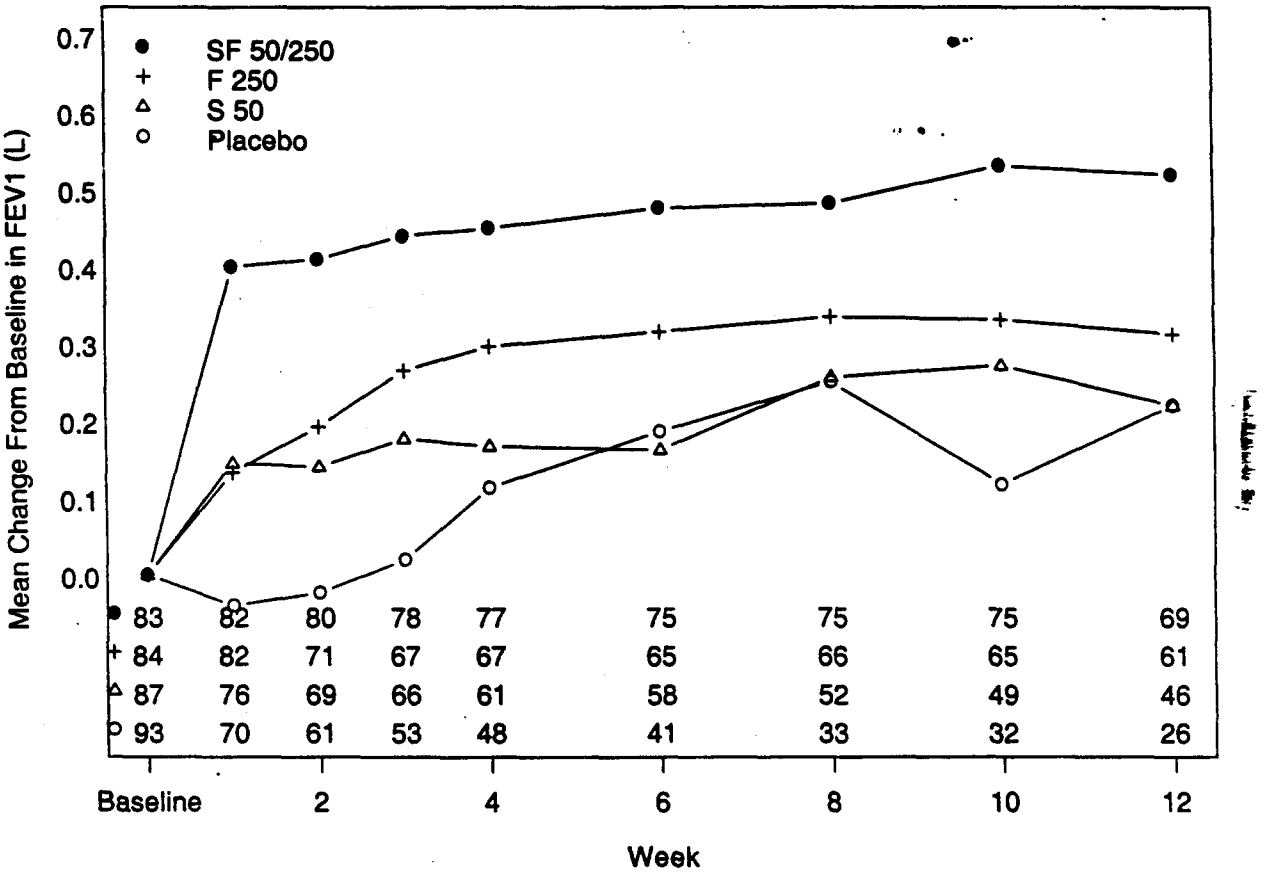
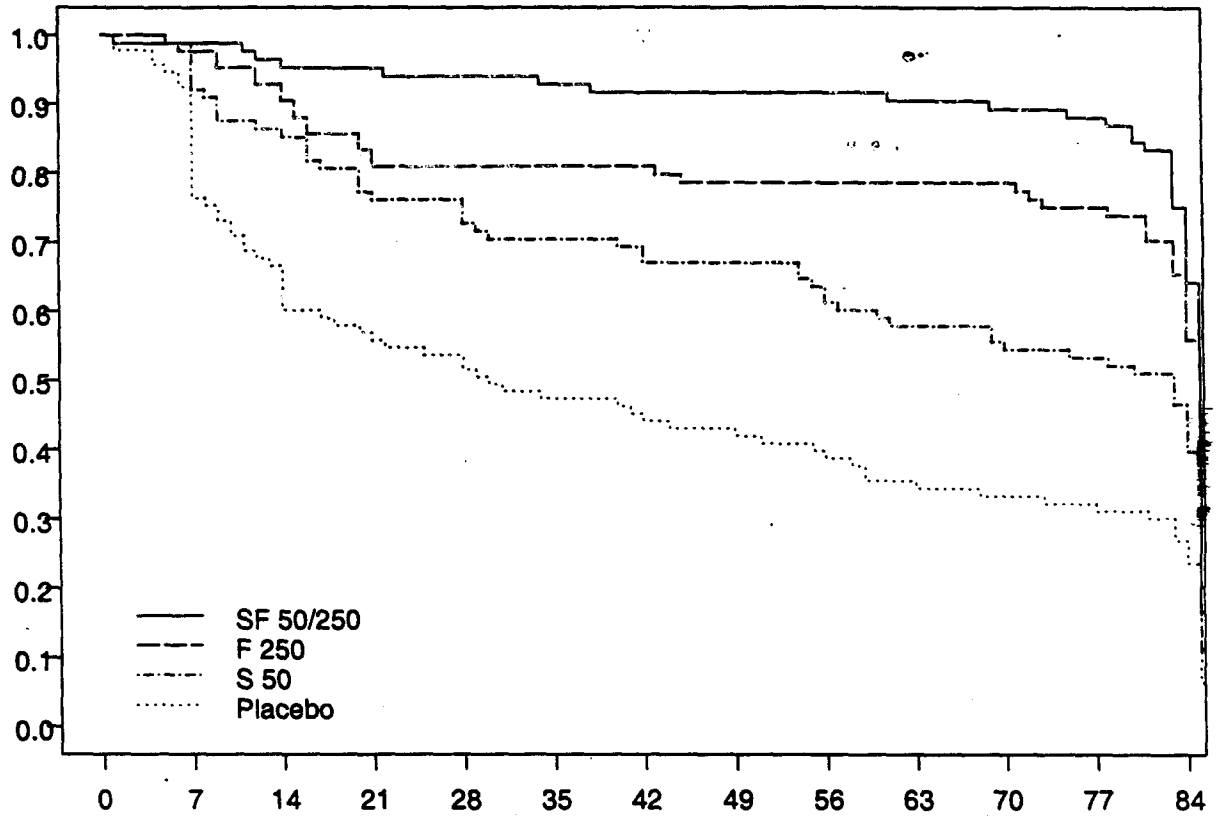
APPENDIX K

Study SFCA3003: Change from Baseline in Morning Predose FEV1 (n)



APPENDIX L

Study SFCA3003: Probability of Patients Remaining in Study



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APPENDIX M

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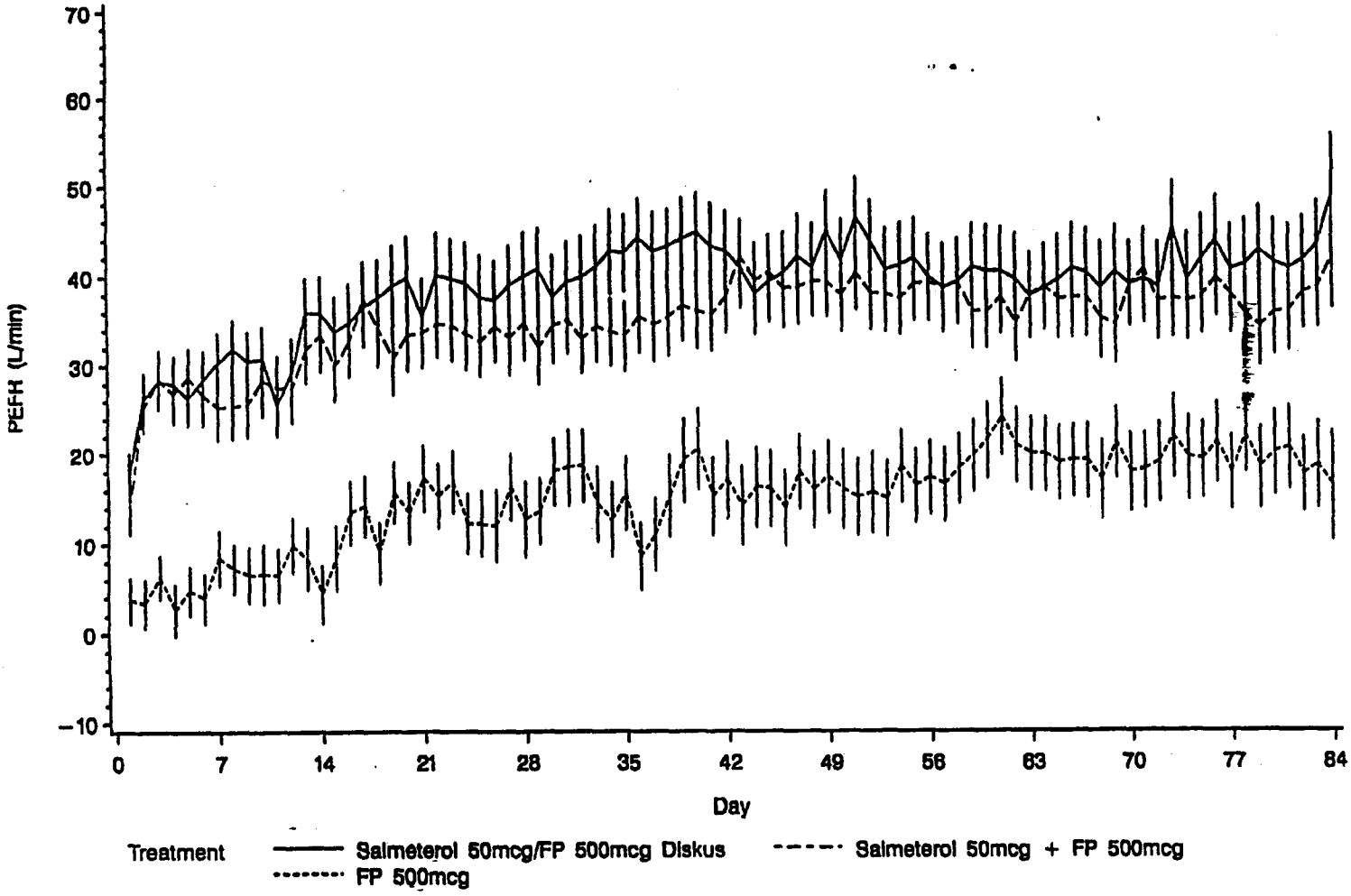
SFCB3019

Change in Mean Morning PEFR (L/min) from Baseline – Daily Means (Intent–to–Treat Population)



Note: Treatment Means +/– 1 standard error

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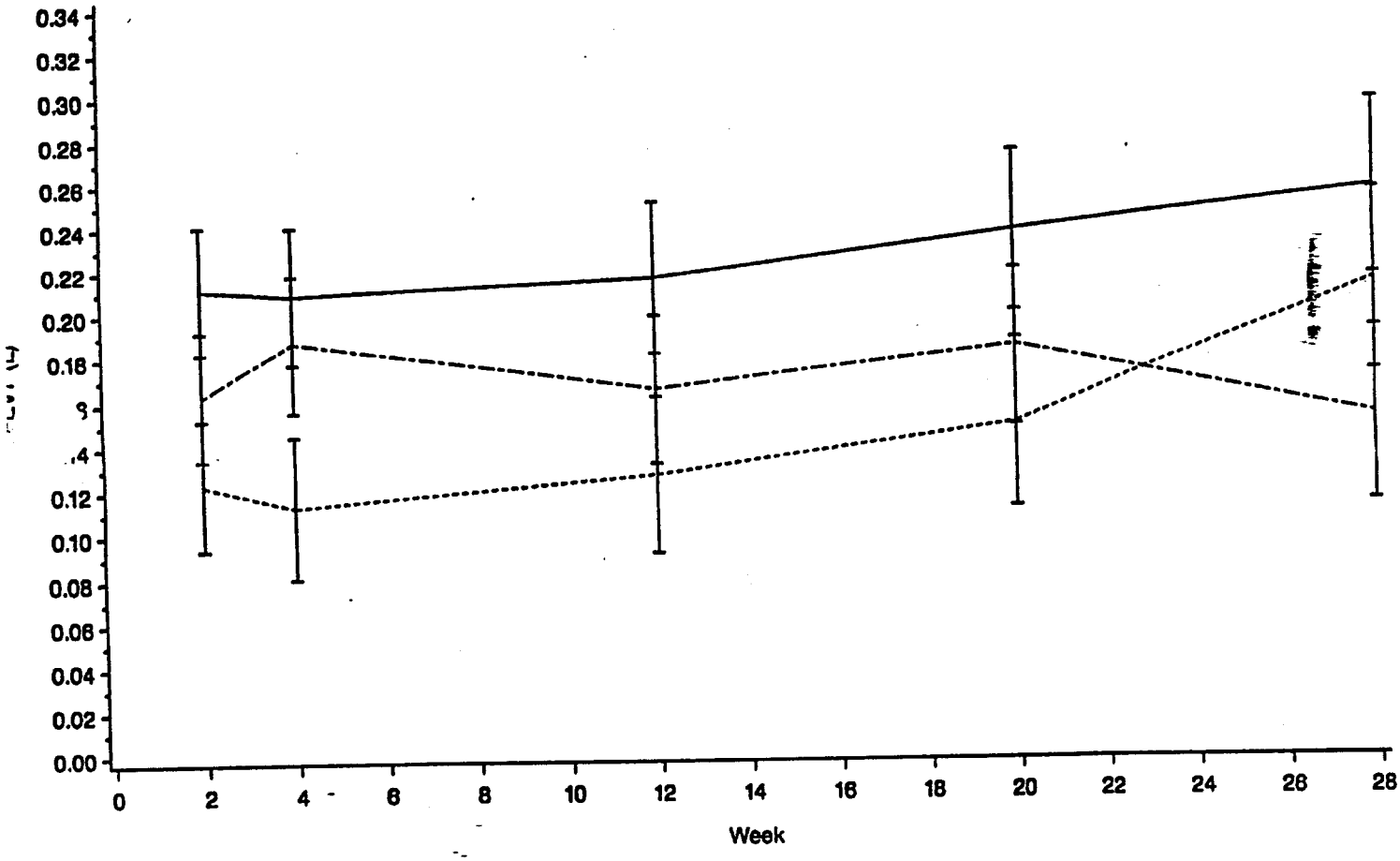
APPENDIX N

APPEARS THIS WAY
ON ORIGINAL

SFCB3019
Clinic Visit FEV1 (L) – Adjusted Mean Change (Intent–to–Treat Population)



Note: Treatment Means +/– 1 standard error

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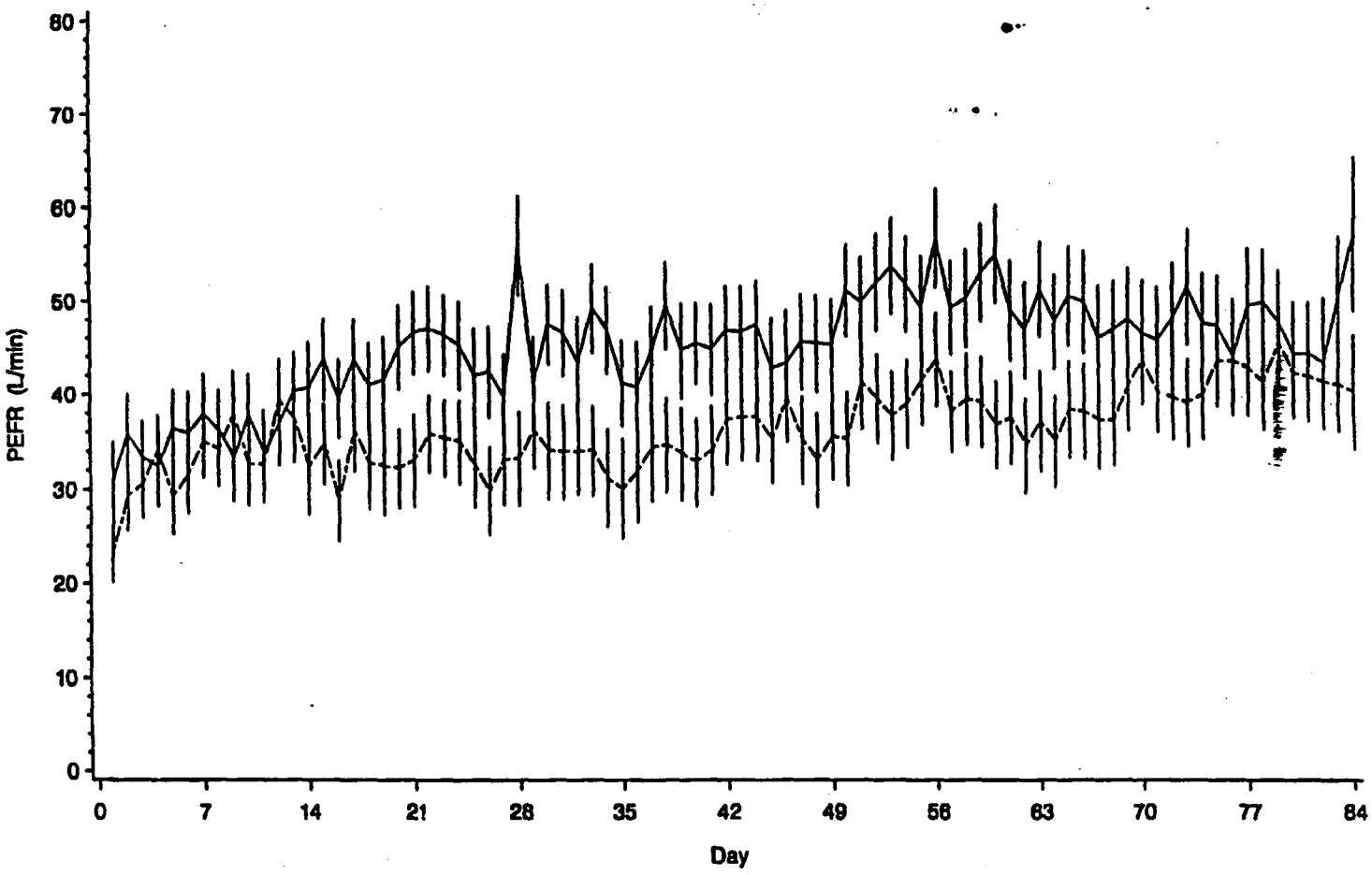
ON ORIGINAL

APPENDIX 0

SFCB3017

Change in Mean Morning PEFR (L/min) from Baseline – Daily Means (Intent–to–Treat Population)



Note: Treatment Means +/– 1 standard error

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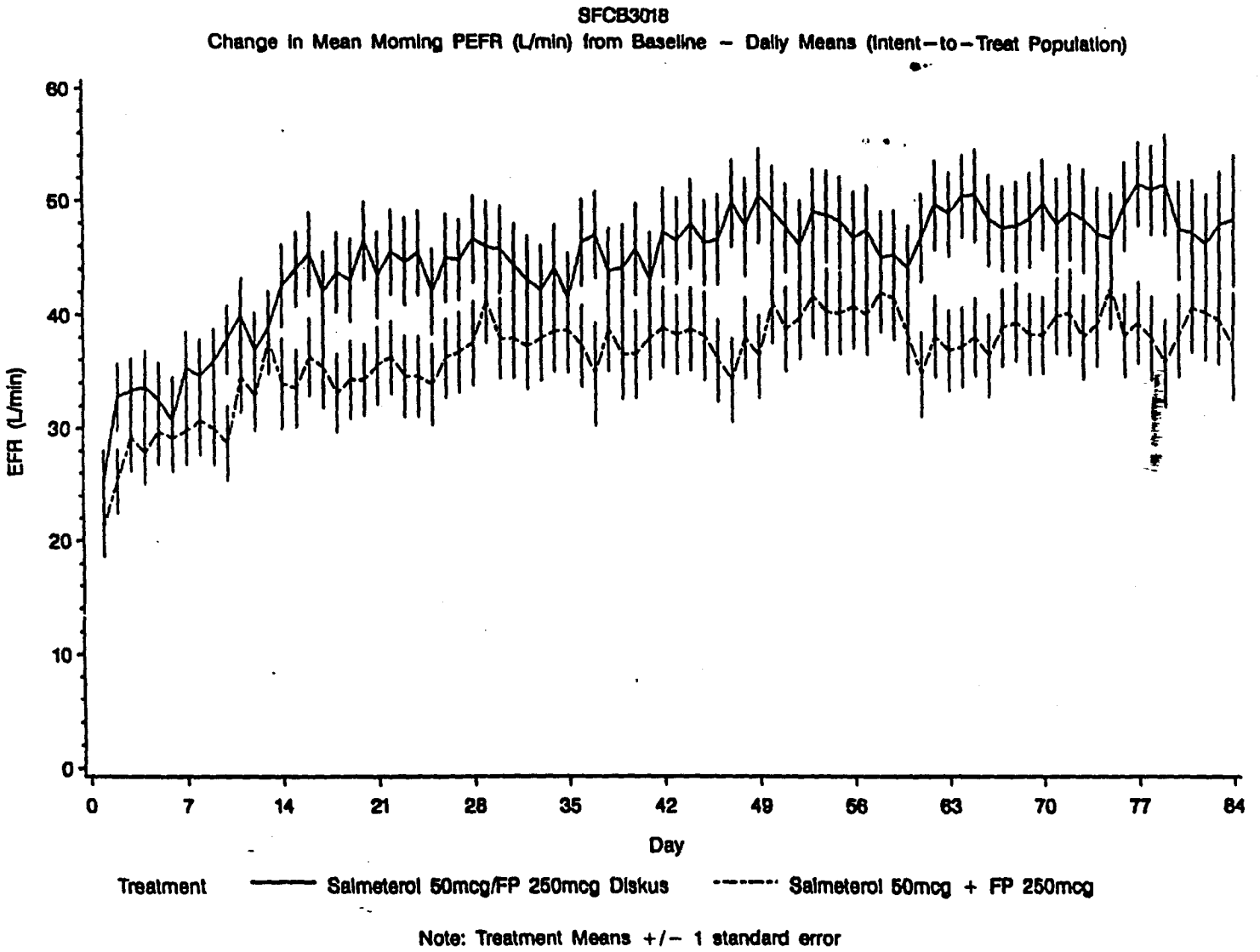
ON ORIGINAL

APPENDIX P



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APPENDIX Q

INTEGRATED SAFETY SUMMARY - ADVERSE EVENTS

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ON ORIGINAL

Adverse Events Occurring at ≥3% in Any Combination Product Treatment Group in Adolescent and Adult Patients					
	PLA n=175	SFC50/100 n=213	SALM50 + FP100 n=123	SALM50 n=180	FP100 n=90
	SFCA3002, SFCA3003	SFCA3002, SFCB3017	SFCB3017	SFCA3002, SFCA3003	SFCA3002
Average duration of exposure (days)	42.3	79.0	79.0	60.1	72.4
Number of patients with any adverse event	86 (49%)	157 (74%)	74 (60%)	108 (60%)	63 (70%)
Ear, nose, & throat (any event)	53 (30%)	105 (49%)	49 (40%)	69 (38%)	44 (49%)
Upper respiratory tract infection	24 (14%)	44 (21%)	18 (15%)	35 (19%)	26 (29%)
Throat irritation	10 (6%)	23 (11%)	9 (7%)	11 (6%)	6 (7%)
Sinusitis	7 (4%)	8 (4%)	4 (3%)	6 (3%)	5 (6%)
Upper respiratory inflammation	9 (5%)	14 (7%)	8 (7%)	15 (8%)	6 (7%)
Rhinitis	1 (<1%)	5 (2%)	7 (6%)	0	0
Hoarseness/dysphonia	1 (<1%)	6 (3%)	4 (3%)	1 (<1%)	2 (2%)
Nasal congestion/blockage	5 (3%)	5 (2%)	1 (<1%)	2 (1%)	1 (1%)
Pharyngitis/throat infections	1 (<1%)	6 (3%)	4 (3%)	4 (2%)	0
Lower Respiratory (any event)	15 (9%)	56 (26%)	26 (21%)	22 (12%)	6 (7%)
Viral respiratory infections	6 (3%)	17 (8%)	9 (7%)	10 (6%)	4 (4%)
Cough	4 (2%)	12 (6%)	4 (3%)	5 (3%)	0
Asthma[a]	2 (1%)	7 (3%)	5 (4%)	2 (1%)	0
Bronchitis	3 (2%)	4 (2%)	3 (2%)	4 (2%)	1 (1%)
Lower respiratory infections	0	18 (8%)	9 (7%)	2 (1%)	0
Breathing disorders	0	1 (<1%)	0	0	0
Neurology (any event)	14 (8%)	33 (15%)	9 (7%)	21(12%)	17 (19%)
Headaches	12 (7%)	26 (12%)	5 (4%)	18 (10%)	13 (14%)
Dizziness	1 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	4 (4%)
Gastrointestinal (any event)	13 (7%)	35 (16%)	14 (11%)	14 (8%)	16 (18%)
Nausea & vomiting	2 (1%)	9 (4%)	2 (2%)	2 (1%)	3 (3%)
Candidiasis mouth/throat	0	3 (1%)	1 (<1%)	0	2 (2%)
Gastroenteritis	0	3 (1%)	3 (2%)	0	0
Diarrhea	2 (1%)	4 (2%)	1 (<1%)	2 (1%)	2 (2%)
Non-site specific (any event)	8 (5%)	19 (9%)	11 (9%)	14 (8%)	12 (13%)
Fever	3 (2%)	3 (1%)	0	5 (3%)	2 (2%)
Chest symptoms	0	3 (1%)	2 (2%)	1 (<1%)	2 (2%)
Exacerbation of condition	0	0	0	0	0
Musculoskeletal (any event)	10 (6%)	16 (8%)	6 (5%)	10 (6%)	5 (6%)
Musculoskeletal pain	5 (3%)	9 (4%)	3 (2%)	5 (3%)	1 (1%)

Source Data: Tables 2.2 and 5.2

[a] Worsening asthma was recorded as an adverse event in the non-US studies.

Adverse Events Occurring at ≥3% in Any Combination Product Treatment Group in Adolescent and Adult Patients (continued)			
	SFC50/250 n=264	SALM50 + FP250 n=192	FP250 n=84
	SFCA3003, SFCB3018[b]	SFCB3018[b]	SFCA3003
Average duration of exposure (days)	150.2	187.9	70.1
Number of patients with any adverse event	219 (83%)	166 (86%)	67 (80%)
Ear, nose, & throat (any event)	143 (54%)	124 (65%)	43 (51%)
Upper respiratory tract infection	84 (32%)	88 (46%)	21 (25%)
Throat irritation	29 (11%)	18 (9%)	9 (11%)
Sinusitis	15 (6%)	15 (8%)	1 (1%)
Upper respiratory inflammation	10 (4%)	8 (4%)	7 (8%)
Rhinitis	10 (4%)	9 (5%)	0
Hoarseness/dysphonia	12 (5%)	7 (4%)	3 (4%)
Nasal congestion/blockage	14 (5%)	13 (7%)	4 (5%)
Pharyngitis/throat infections	7 (3%)	8 (4%)	1 (1%)
Lower Respiratory (any event)	103 (39%)	83 (43%)	12 (14%)
Viral respiratory infections	44 (17%)	31 (16%)	8 (10%)
Cough	22 (8%)	29 (15%)	0
Asthma[a]	24 (9%)	18 (9%)	1 (1%)
Bronchitis	19 (7%)	10 (5%)	2 (2%)
Lower respiratory infections	10 (4%)	5 (3%)	0
Breathing disorders	7 (3%)	12 (6%)	0
Neurology (any event)	55 (21%)	41 (21%)	10 (12%)
Headaches	45 (17%)	33 (17%)	7 (8%)
Dizziness	7 (3%)	4 (2%)	0
Gastrointestinal (any event)	52 (20%)	44 (23%)	15 (18%)
Nausea & vomiting	12 (5%)	10 (5%)	3 (4%)
Candidiasis mouth/throat	13 (5%)	10 (5%)	2 (2%)
Gastroenteritis	9 (3%)	5 (3%)	0
Diarrhea	7 (3%)	5 (3%)	2 (2%)
Non-site specific (any event)	36 (14%)	41 (21%)	7 (8%)
Fever	8 (3%)	9 (5%)	1 (1%)
Chest symptoms	11 (4%)	8 (4%)	0
Exacerbation of condition	2 (<1%)	0	0
Musculoskeletal (any event)	28 (11%)	21 (11%)	8 (10%)
Musculoskeletal pain	16 (6%)	13 (7%)	4 (5%)

Source data: Tables 2.2 and 5.2

a Worsening asthma was recorded as an adverse event in the non-US studies

b 28-week study

JUN 2 3 1999

Medical Officer Filing Review

Division of Pulmonary Drug Products (HFD-570)

Application #:	NDA 21-077	**Category of Drug:**	Combination: Long Acting Beta Agonist and Corticosteroid
Sponsor:	GlaxoWellcome	**Route of Administration:**	Oral Inhalation
Proprietary Name:	Advair	**Medical Reviewer:**	Susan Johnson, Ph.D.
USAN/Established Name:	Salmeterol/ Fluticasone Proprionate	**Review Date:**	June 21, 1999

Submissions Reviewed in This Document

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
March 24, 1999	March 29, 1999	Original NDA	

Related Applications (if applicable)

Overview of Application and Review:
Application is fileable.

Outstanding Issues:
DSI inspection request should be issued.

Recommended Regulatory Action

New Clinical Studies: _____ Clinical Hold
_____ May Proceed

NDA/Supplements: _____ Approval
_____ Approvable

Signature Medical Reviewer **Date:** 6/21/99

Concurrence: /S/ , Acting DivDir **Date:** 6/23/99

cc: Div File
NDA 21-077

Overview:

The sponsor has proposed marketing three combination formulations:
Advair Diskus ——— – salmeterol /fluticasone propionate 50/100 mcg
Advair Diskus ——— – salmeterol /fluticasone propionate 50/250 mcg
Advair Diskus ——— – salmeterol /fluticasone propionate 50/500 mcg.

The combination of these previously-approved, twice-daily, single ingredient regimens into a single product is based primarily on the sponsor's interest in enhancing convenience for asthma patients who require both long acting beta agonist and orally inhaled corticosteroid treatment. Three strengths have been developed in order to allow for titration of the fluticasone propionate dose. Currently, Flovent Rotadisk is approved for doses ranging from 100 mcg to 500 mcg twice daily.

The sponsor indicates at least some of products are currently approved in 14 European nations, including the United Kingdom, although limited marketing experience is available given that the first approval was in Sweden in September, 1998.

Proposed Indications:

The proposed indication for each product is for the maintenance treatment of asthma ——— in patients age 12 years and older.

———————————————, although the sponsor has conducted a trial of Advair 100 mcg in patients age 4 to 11 years (SFCB3020).

Formulation:

Each disposable Diskus device contains 60 blisters. A sample/institutional size is available with 28 blisters. Each blister contains active drug substance (72.5 mcg ——— salmeterol xinafoate equivalent to 50 mcg of salmeterol base plus either 100, 250 or 500 mcg ——— fluticasone propionate) and lactose ——— a total of 12.5 mg. Lactose ———————————— ———

Efficacy:

There are three pivotal efficacy trials contained in this submission, Trials SFCA3002, SFCA3003, and SFCB3019. The first two trials, 3002 and 3003 compared combination Advair product, containing 50 mcg salmeterol and fluticasone propionate doses of 100 mcg and 250 mcg, respectively, to the same doses of salmeterol or fluticasone propionate administered as single ingredient products. These were randomized, double-blind, placebo controlled trials with fours parallel treatment groups. The duration of each trial was 12 weeks, both utilized a placebo control and both were conducted at multiple sites in the U.S. The population of each trial had screening FEV_1 values between 40 an 85 percent of predicted. Patients in Trial 3002 were stratified by prior

corticosteroid use, while all patients in trial 3003 were required to have used corticosteroids in the past.

These trials were designed, in part, to address the combination policy for fixed-combination prescription drug products (CFR § 300.50) and establish that the efficacy of salmeterol and fluticasone administered as a combination product exceeds the efficacy of the individual ingredients administered alone. The primary endpoint was change from baseline FEV_1.

The third pivotal trial was Trial 3019 and was designed to compare three treatments: the combination of 50 mcg salmeterol / 500 mcg fluticasone propionate, 500 mcg fluticasone propionate alone, and 50 mcg salmeterol plus 500 mcg fluticasone propionate, administered concurrently as single ingredient products. This trial was 28 weeks in duration and was conducted in Germany, France and the Netherlands.

Two supporting trials, SFCB3017 and 3018 were conducted to compare Advair 100 mg and Advair 250 mcg, respectively, to the single ingredient products used concurrently. A study of similar design, SFCB3020, was conducted in pediatric patients, age 4 to 11 years, with Advair 100 mcg. All three of these trials were conducted outside of the U.S. and were 12 weeks in duration.

Safety:

The five adult and one pediatric clinical trials described above constitute the safety database for this application. Of the adult trials, Trials 3002, 3003 and 3017 were 12 weeks in duration, while Trials 3018 and 3019 were 28 weeks in duration. A total of 1824 patients were included in these trials. These data are adequate to support filing and review.

Filing Issues:

In addressing the fixed-combination policy in 21 CFR 300.50, it is noted that there is one treatment comparison omitted from the array of trial designs, specifically the comparison of Advair 500 mcg to salmeterol 50 mcg. This is acceptable, given that the other doses were studied with a "complete" design and pharmacokinetic data may help to link the three formulations (see Review Issues).

The submission appears to be complete upon cursory examination and is presented in an organized fashion.

Review Issues:

The sponsor should be asked to identify which of the three products has been approved in foreign markets (i.e., where all three strengths have been approved) and to indicate which products are currently marketed.

The sponsor should also be asked to describe the color of each inhaler and the mechanism in which the three strengths can be distinguished from one another and from other Diskus products.

Dose proportionality was not directly established in this development program, although pharmacokinetic data are available for all strengths. Dose proportionality was established in the Flovent development program and extrapolation may be possible.

The Pulmonary-Allergy Drugs Advisory Committee may be asked to address questions regarding the utility of a fixed-dose combination in clinical practice, e.g. whether the combination is rational, given the limited flexibility in dose titration.

Percent of predicted FEV_1 was defined in these trials, including the U.S. trials, based on the guidelines of the "Working Party of the European Community for Coal and Steel." These data should be evaluated carefully relative to the conventional U.S. approaches.

Auditing:

Given that the sponsor has studied approved doses of both ingredients, the Division of Scientific Investigation (DSI) will be asked to conduct minimal auditing of clinical trials. It is known that Dr. Thomas Edwards, now a disqualified investigator, participated in Trials 3002 and 3003. The trial were analyzed with and without data from his site and the outcomes were not substantially changed.

Given their pivotal status, it is most appropriate to audit the U.S. trials. These trials are largely similar in design. Since a higher product strength was associated with Trial 3003 (Advair 250), relative to Trial 3002 (Advair 100), there is potentially more safety information associated with Trial 3003. A list of the 39 investigator sites associated with Trial 3003 is attached. No single investigator site enrolled more than six percent of the study population (range, between 1 and 21 of the total 349 patients) or was likely to have driven the statistical outcomes. The largest number of patients were enrolled at the following sites:

P. Chervinsky	**(N = 21)**
J. Pinnas	**(N = 19)**
H. Windom	**(N = 19)**
J. Taylor	**(N = 17)**

Ms. Jani, the project manager for this application, will be asked to forward this list to DSI in order that they determine which, if any, of the largest investigator sites has not recently been audited. The final selection should be made in conjunction with the DSI assessment and it is recommended that a single site be selected. Additional clinical data from the application can be provided to DSI when they have selected an investigator site for inspection.

Conclusion:

This application is fileable. This decision was made in preparation for the review team meeting on April 23, 1999 and is currently being documented via this review.

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