

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Review No. 3

IND Number: 53,391

Serial Number(s): N (MR)

Date(s) of Submission: Letter Date: August 26, 1997
CDER Stamp: August 28, 1997

Information to be Conveyed to Sponsor: Yes (X), No ()

Reviewer: Satish C. Tripathi, Ph.D.

Date Review Completed: November 05, 1997

Sponsor: Byk Gulden Lomberg Chemische Fabrik
GmbH, Postfach 10 03 10, 78403
Konstanz, Germany (Dr. Petra
Willersinn-Kern:
Tel: 011-49-7531-84-2837).

Sponsor (U.S. Representative): Altana Inc., 60 Baylis Road, Melville,
NY 11747 (Miss Virginia Carman:
516-454-7677 Extension 2091).

Manufacturer: _____

Drug Name: Primary: Ciclesonide
Other Names: Byk Gulden B9207-015

Chemical Name: [11 β , 16 α (R)]-16, 17-[Cyclohexyl-
methylene) bis(oxy)-11-hydroxy-21-
(2-methyl-1-oxopropoxy) pregna-1, 4-
diene-3, 20-dione.

CAS Number: 141845-82-1

b(4)

Molecular Weight and Formula: 540.7; C₃₂H₄₄O₇

Related INDs/NDAs/DMFs: DMF — Toxicology testing of HFA-134a (MDI Propellant) ————— **b(4)**

Class: Glucocorticoid Steroid.

Indication: Mild to moderate chronic asthma.

Clinical Formulation: White to off-white powder available as MDI that delivers — 100, and 200 µg (ex valve) per puff. Other ingredients: ' — (w/w) propellant HFA-134a and — (w/w) ethanol. **b(4)**

Route of Administration: Inhalation (via MDI).

Previous Submission, Review Date and Reviewer:

Date of Submission	Reviewer	Review Date
05/23/97	Satish Tripathi	08/01/97
05/23/97	Satish Tripathi	09/05/97

Studies Reviewed in this IND:

TOXICOLOGY
1. Rat: 4-wk Inhalation Toxicity (MDI-HFA Formulation), Vol. A4.2
2. Dog: 4-wk Inhalation Toxicity (MDI-HFA Formulation), Vol. A4.3 - 4.4
3. Draft Protocol: 13-wk Inhalation Toxicity (MDI-HFA Formulation) Study in Dogs, Vol. A. 4.1
4. Response to Our Letter of August 12, 1997

Note: Portions of this review were excerpted directly from the sponsor's submission.

TOXICOLOGY**Rat: 4-wk Inhalation Toxicity Study with MDI (HFA) Formulation**

Byk Gulden Study 92E/97, 04 July, 1997, Vol. A4.2

Study Dates: 29 October, 1996 to 04 July, 1997*Testing Lab:* _____**b(4)**

Test Article: Ciclesonide (Batch CT960812) administered to the animals via Aerosol Generator System MDI 3000 (_____) . The drug product consisted of drug substance in a Vehicle containing _____ (w/w: _____ mg/shot) ethanol and HFA-134a (% not known; _____ mg/shot) and _____ impurities.

GLP: Signed GLP Statement was included.**METHODS***Species/Strain:* Wistar rats [_____: WI(WU)BR].**b(4)***Animals:* 70/Sex; 10/Sex/group.*Route:* Inhalation (nose only).

Dosage: Air Control; Vehicle Control; 18 µg/kg/day (LD); 53 µg/kg/day (MD); 164 µg/kg/day (HD); Air Control Recovery; HD Recovery. The drug or vehicle was delivered using an aerosol. Aerosol was sprayed in a mixing chamber and diluted by air. Air flow rates were adjusted to valve about 10 to 30 L/min. The dose was calculated with a respiratory minute volume $V_{min} = 2.1 \times (\text{body weight})^{0.75}$, 1 h respiratory volume (VR) = $60 \times V_{min}$, actual mean body weights and aerosol concentration (1.11, 3.24, and 9.95 mg/m³ for LD, MD, and HD, respectively), 50% deposition, and 100% resorption of the inhaled particles.

Duration of Exposure: 4 weeks (1 hour/day; 7 days/week).*Clinical Observations:* Daily (before, during, and after exposure); detailed examination was conducted weekly.*Body Weights:* Weekly.*Food Consumption:* Weekly.*Ophthalmoscopy:* Prior to beginning study, at the end of exposure period and at the end of recovery period.*Hematology:* Days -7, 28, and 56 (recovery groups).*Clinical Chemistry:* Days -7, 28, and 56 (recovery groups).

Urinalysis: Days -7, 28, and 56 (recovery groups). Urinalysis parameters were determined for Air Control and HD groups only except for osmolarity. Rationale for not determining urinalysis parameters for LD, MD, and Vehicle Control groups was not provided.

Drug Plasma Levels: Blood samples collected but not analyzed.

Organ Weights, Gross- and Histopathology: At termination. Determination of organ weights were limited to adrenals, heart, kidney, liver, lung, spleen, testes, and thymus. Histopathology was done on all tissues.

RESULTS

Mortality: There was no mortality during the course of the study.

Clinical Signs: No toxicologically significant treatment-related effects.

Body Weights: Treatment resulted in decreased body weight gains (σ : LD 14%, MD 39%, HD 62%; Vehicle Control: 15%; HD Recovery group on Day 56: 12%; ♀ : LD 16%, MD 74%; Vehicle Control: 12.7%) or body weight loss (♀ : HD 1.2%). Decrease in body weights was as follows: σ : LD 2.5%, MD 7.3%, HD 12%; Vehicle Control: 2.1%; HD Recovery group on Day 56: 2.5%; ♀ : LD 2%, MD 8.3%, HD 9.8%; Vehicle Control: 1.3%; Recovery group on Day 56: 2%.

Food Consumption: Treatment resulted in decreased food consumption (σ : MD 10%, HD 15%) during the last week of treatment.

Ophthalmoscopy: No toxicologically significant treatment-related effects.

Hematology: No toxicologically significant treatment-related effects.

Clinical Chemistry: No toxicologically significant treatment-related effects.

Urinalysis: Treatment resulted in increased urinary osmolarity in females (MD 52%, HD 78%); increased creatinine (σ : HD 12%; ♀ : HD 66%); increased sodium (σ : HD: 11%; ♀ : HD: 2.6-fold), potassium (♀ : HD 79%), calcium (σ : HD 69%; ♀ : HD: 5.4-fold), and chloride (♀ : HD 2.4-fold); and decreased phosphate (σ : HD: 8.3-fold with high standard deviation; ♀ : HD 64%). Data on LD, MD, and Vehicle Control groups were not available except for osmolarity.

Organ Weights: Treatment resulted in decreased relative weights of thymus (σ : LD 10%, MD 34%, HD 42%; ♀ : MD 25%, HD 51%) which was reversible.

Gross Pathology: Reduction in the size of thymus was seen at MD and HD (both sexes).

Histopathology: Drug-related changes are indicated in Table 1:

Table 1. Histopathologic Findings in a 4-wk Rat Study with HFA Formulation

Finding	Air Control	Vehicle Control	LD	MD	HD	Recovery Air Control	Recovery HD
Thymus: Cortical atrophy ♂	0/10	1/10	0/10	5/10	10/10	0/10	0/10
♀	0/10	0/10	1/10	4/10	10/10	1/10	3/10
Spleen: Lymphoid depl. ♂	0/10	0/10	0/10	1/10	4/10	0/10	0/10
♀	0/10	0/10	0/10	0/10	2/10	0/10	0/10

Based on decrement in bodyweight and changes in urinary parameters, relative thymus weights, and incidence and severity of histopathologic change in thymus and spleen, the NOAEL for this study is 53 µg/kg/day.

The sponsor should be asked to provide rationale for not determining urinalysis parameters for LD, MD, and Vehicle Control groups in the 4-week rat study with MDI (HFA) formulation.

APPEARS THIS WAY ON ORIGINAL

Dog: 4-wk Inhalation Toxicity Study with MDI (HFA) Formulation

Byk Gulden Study 103/97, 16 July, 1997, Vol. A4.3 - 4.4

Study Dates: 27 January, 1997 to 05 May, 1997*Testing Lab:* Byk Gulden Institute of Pathology and Toxicology, Germany.*Test Article:* Ciclesonide (Batch CT960810) generated from MDIs fitted with a 50 μL /shot valve. The drug product consisted of drug substance in a Vehicle containing (w/w; mg/shot) ethanol and HFA-134a (% not known; mg/shot) and % impurities.*GLP:* Signed GLP Statement was included.

b(4)

METHODS*Species/Strain:* Dog (Beagle).*Animals:* 20/Sex; 4/Sex/group: Vehicle Control, LD, MD, and HD; 2/Sex/group: HD Recovery groups (weeks 4 and 8).*Route:* MDI aerosol (head only inhalation).*Dosage:* Vehicle Control; 19 $\mu\text{g}/\text{kg}/\text{day}$ (LD); 61 $\mu\text{g}/\text{kg}/\text{day}$ (MD); 118 $\mu\text{g}/\text{kg}/\text{day}$ (HD); and HD Recovery groups sacrificed at 4 and 8 weeks after dosing. Dose calculation was based on following assumptions: body weight=10 kg, respiratory minute volume in the dog=5L/min., exposure duration=30 min., deposition of drug substance in respiratory tract=50%; following formula was used:

$$\text{mean calculated dose (mg/kg)} = \frac{5 \text{ L/min} \times 30 \text{ (min)} \times \text{mean aerosol conc.} * \times 0.5}{10 \text{ (kg)} \times 1000}$$

Mean aerosol concentration for LD, MD, HD, and HD Recovery groups were 2.7, 8.2, 15.5, and 15.9 $\mu\text{g}/\text{L}$, respectively. Seventy percent of the particles had aerodynamic diameter of μm .

b(4)

Duration of Exposure: 28 days (30 min. daily).*Clinical Observations:* Daily; detailed examinations performed once pre-study and at the end of 4, 8, and 12 weeks (8 and 12 for recovery groups only).*Body Weights:* Day -4 and twice a week during treatment.*Food Consumption:* Daily.*Ophthalmoscopy:* Week 1, 4, and 8 (recovery group animals only).*Electrocardiography:* Week 1, 4, 8, and 12 (8 and 12 for recovery groups only). Studied parameters were heart rate, P-wave, PQ, QRS, QT, and amplitude; bipolar leads, unipolar limb leads, and unipolar precordial chest leads were used.*Respiratory Function:* Week 1, 4, 8, and 12 (8 and 12 for recovery groups only).

Respiratory rate, tidal volume, and respiratory minute volume were studied.

Hematology: Twice pre-study and at Week 1, 4, 8, and 12 (8 and 12 for recovery groups only).

Clinical Chemistry: Twice pre-study and at Week 1, 4, 8, and 12 (8 and 12 for recovery groups only).

Urinalysis: Once pre-study and at Week 4, 8, and 12 (8 and 12 for recovery groups only).

Drug Plasma Levels: Samples were collected but not analyzed.

Organ Weights, Gross- and Histopathology: At termination. Complete battery of organ weights and histopathology of organs was performed.

RESULTS

Mortality: There were no mortalities.

Clinical Signs: No toxicologically significant treatment-related effects.

Body Weights: No toxicologically significant treatment-related effects.

Food Consumption: No toxicologically significant treatment-related effects.

Ophthalmoscopy: No toxicologically significant treatment-related effects.

Electrocardiography: No toxicologically significant treatment-related effects.

Respiratory Function: No toxicologically significant treatment-related effects.

Hematology: No toxicologically significant treatment-related effects.

Clinical Chemistry: No toxicologically significant treatment-related effects.

Urinalysis: No toxicologically significant treatment-related effects.

Organ Weights: No toxicologically significant treatment-related effects.

Gross Pathology: No toxicologically significant treatment-related effects.

Histopathology: Drug-related changes are indicated in Table 2:

Table 2. Histopathologic Findings in a 4-wk Dog Study with HFA Formulation

Histopathologic Finding	Control	LD	MD	HD	Recovery 4 wk	Recovery 8 wk
Thymus: Cortical atrophy ♂	0/4	0/4	0/4	4/4	0/2	0/2
♀	0/4	0/4	0/4	4/4	0/2	0/2
Spleen: Loss sec. foll. ♂	0/4	0/4	0/4	2/4	0/2	0/2
♀	0/4	0/4	0/4	4/4	0/2	0/2
Adrenals: Atrophy of Zona fasciculata ♂	0/4	0/4	0/4	2/4	0/2	0/2
♀	0/4	2/4	2/4	3/4	0/2	0/2
Lym. nodes: Loss sec. foll. ♂	0/4	0/4	0/4	3/4	0/2	0/2
♀	0/4	0/4	0/4	1/4	0/2	0/2

Based on histopathologic findings in thymus, spleen, adrenals, and lymph nodes, the NOAEL in this study is 61 µg/kg/day.

Draft Protocol: 13-wk Inhalation Toxicity (MDI-HFA Formulation) Study in Dogs, Vol. A. 4.1

Although a 13-week inhalation study in an appropriate species is generally required to bridge between DPI and MDI formulations, the sponsor was advised, in a meeting on September 17, 1997, to consider long-term study of 6 month duration in rat. This was based on incidence of alveolar histiocytosis in the lung in 6-month rat study with DPI and findings of the nasal cavity in the 12 month dog study with DPI; findings of nasal cavity in the 12 month dog study could be a local effect due to the method of drug delivery and would not be relevant to the proposed human use. Sponsors stated that a 12 month oral study in dog will support the irrelevancy of this finding (during the meeting of 09/17/97). Thus, a toxicity study is needed to establish safety profile of the MDI formulation of the drug (and not merely bridge DPI data with data from MDI formulation); this study should be of 6 months duration. Function (mobility, phagocytosis, etc) of alveolar histiocytes (macrophages) in BAL (bronchoalveolar lavage) samples should be studied after 6 month exposure period. A DPI arm would be needed in the 6 month study.

Response to FDA Letter of August 12, 1997

The following is a brief summary of conclusions from the Division of Pulmonary Drug Products meeting with Byk Gulden on September 17, 1997 (please see meeting minutes for full text of discussions):

1a) Comment on 4-week toxicity studies in rats and dogs (MDI formulation):

The FDA pointed out that the species used in rat study with MDI (HFA) formulation (4-wk) was Wistar while the one used with DPI formulation (4- and 26-wk) was Sprague-Dawley. Byk Gulden stated that during earlier studies, due to worldwide viral infection, Wistar species could not be used as it was not possible to obtain rats free of infection. The sponsor was advised that future toxicity studies in rat (if needed) should be conducted in Sprague-Dawley strain.

The Agency asked ByK Gulden to verify whether or not use of HFA-123a indicated in the Summary section of the 4 wk rat study with MDI (HFA) is a typographical error.

1b) Comment on Draft Protocol for 3 month dog study:

The FDA advised that long-term toxicity study with MDI (HFA) formulation should be a 6-month study in rat. This decision was based on findings of alveolar histiocytosis in the 6-month rat study and findings of nasal cavity in the 12-month dog study. It was agreed that if Byk Gulden can produce evidence that can satisfactorily deal with the issues raised from histopathologic findings in 6-month rat and 12-month dog studies with DPI formulation, Byk Gulden would not be required to conduct 6-month rat study with MDI (HFA) formulation and may instead do a 3-month study with MDI (HFA) formulation and, depending upon the evidence to be provided by Byk Gulden, the 3 month study could even be in dog.

1c) Comment on Histopathologic findings:

The Agency stated that in the 6-month rat study with DPI formulation, finding of alveolar histiocytosis could not be considered as a typical background lesion for this strain (Sprague-Dawley) because supporting evidence (e.g., historical data) was not provided. The Agency reiterated that the incidence of alveolar histiocytosis with "slight" grade showed drug-related effect. It was decided that the sponsor will provide evidence to support that the finding of alveolar histiocytosis is due to background and is not a drug-related effect.

The Agency stated that in the 12-month dog study with DPI formulation, incidences of osteofibrosis and chondrosis were not reversible and could not be considered as background noise due to lack of supporting evidence (e.g., historical controls). Byk

Gulden was asked to provide evidence to support that these drug-related findings represent only local effect and not systemic effect. The sponsor stated that a 12 month study in dogs recently completed will support their conclusion. The sponsor will provide report of recently completed 12-month dog study.

1d) Comment on toxicokinetic data:

The Agency pointed out that toxicokinetic data were still incomplete.

1e) Comment on toxicity studies with CFC formulation:

The Agency stated that since bridging from CFC to HFA-134a formulation was not an issue, the non-GLP nature of studies with CFC formulation and non-availability of pulmonary deposition data are also not issues at this time. Byk Gulden was advised that, in future, non-GLP studies that are to be used for safety assessment, deviations from GLP should be indicated.

1f) Comment on the incidence of alveolar microhemorrhage in 4 wk dog study and interchange of thymus and thyroid data:

The Agency stated that the sponsor's explanations were acceptable.

OVERALL SUMMARY AND EVALUATION

Toxicology: In rats, 4-week inhalation administration of the drug with MDI (HFA) formulation resulted in decreased body weight gains (dose dependent); food consumption decreased (MD and HD males only) only during the last week of treatment. Treatment also resulted in increased levels of urinary osmolarity ((MD and HD females only), creatinine (HD), sodium (HD), potassium (HD females only), and chloride (HD females only) and decreased levels of phosphates (HD). There was dose dependent decrease in relative weights of thymus and increase in the incidence of cortical atrophy of thymus and lymphoid depletion of spleen. Effect of drug on thymus cortex was not completely reversible. The NOAEL for this study was 53 µg/kg/day and the target organs of effect were thymus and spleen. The sponsor should provide rationale for limiting organ weight determination to adrenals, heart, kidney, liver, lung, spleen, testes, and thymus. The sponsor should also provide rationale for not determining urinalysis parameters for LD, MD, and Vehicle Control groups in the 4-week rat study with MDI (HFA) formulation.

In dogs, 4-week inhalation of the drug with MDI (HFA) formulation resulted in cortical atrophy of thymus (HD), loss of secondary follicles in spleen (HD), atrophy of zona fasciculata of adrenals (HD males and dose dependent in females), and loss of secondary follicles of lymph nodes (HD). All these changes were reversible. The NOAEL for this study was 61 µg/kg/day and the target organs of effect were thymus, spleen, adrenals, and lymph nodes.

Response to FDA Letter of August 12, 1997: The following statements resulted from our review of sponsor's comments which were provided to us in response to FDA letter of August 12, 1997:

In the meeting on 9/17/97, the sponsor agreed to:

1. conduct future toxicity studies in rat (if needed) in Sprague-Dawley strain.
2. check their records to verify whether or not use of HFA-123a indicated in the Summary section of the 4 wk rat study with MDI (HFA) formulation is a typographical error.

3. provide evidence to support that the finding of alveolar histiocytosis in 6-month rat study with DPI formulation is due to background and is not a drug-related effect. The sponsor will provide report of recently completed 12-month dog study to support that the drug-related findings in nasal cavity in a previous 12-month dog study with DPI formulation represent only local effect and not systemic effect. If the evidence would be found to be satisfactory, Byk Gulden would not be required to conduct 6-month rat study with MDI (HFA) formulation and may instead do a 3-month study with MDI (HFA) formulation in an appropriate species that could even be dog.
4. provide all toxicokinetic data.
5. indicate deviations from GLP for future non-GLP studies that are to be used for safety assessment.

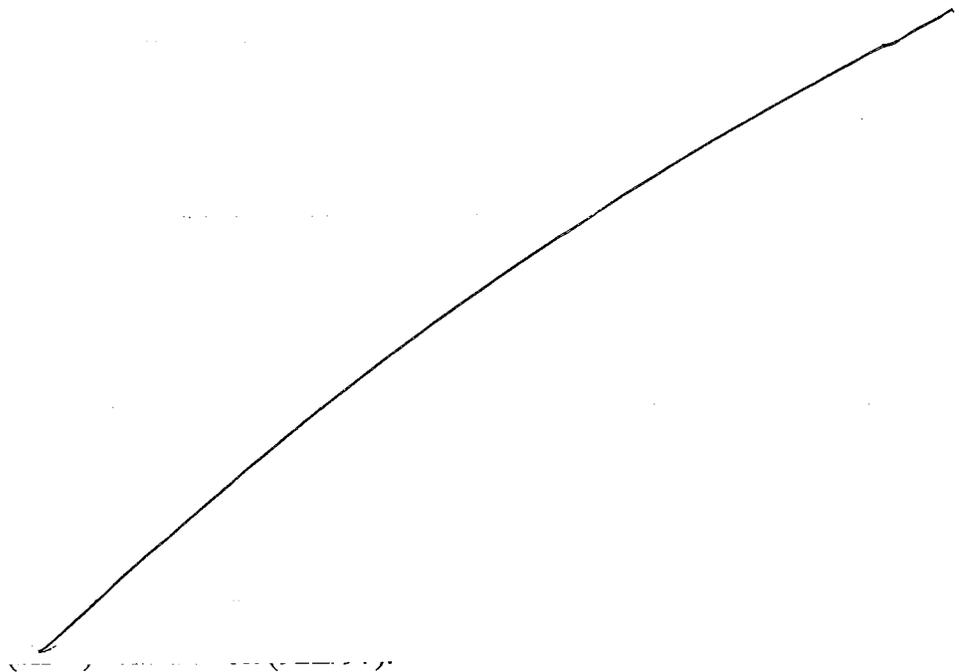
Clinical Dose: Toxicity studies of 4 weeks duration with MDI (HFA) formulation resulted in NOAEL of 53 µg/kg/day in rats and 61 µg/kg/day in dogs. With a safety factor of 10 for rats and 6 for dogs taken into account, clinical dose could be 5.3 or 10.2 µg/kg/day. However, based on long-term toxicity studies with DPI formulation, rat is more sensitive species than dog. Therefore, based on preclinical data, top starting initial clinical dose should be limited to 5.3 µg/kg/day for a duration of 4 weeks. The proposed clinical daily dose of 800 µg (16 µg/kg/day) is not supported by preclinical data. The Medical Reviewer will decide whether a clinical dose of 16 µg/kg/day for a duration of 4-week would be supported by 12-wk clinical study conducted in Europe.

RECOMMENDATION

The proposed clinical daily dose of 800 µg (16 µg/kg/day) is not supported by preclinical data. The Medical Reviewer will decide whether a clinical dose of 16 µg/kg/day for a duration of 4-week would be supported by 12-wk clinical study conducted in Europe. Since no sufficient preclinical data are available to support the clinical dose for study of up to 3 months. Thus, it would have to be based on previous human data. Data to determine NOAEL in the long-term (≥ 3 months) toxicity study with MDI formulation should be available for review prior to initiating the clinical trial of greater than 3 months.

Based on preclinical data available thus far, the sponsor should conduct a 6 month study in rats to establish safety profile of the MDI formulation of the drug and to bridge between MDI and DPI formulations. Rationale should be provided for not determining weights of all organs and urinalysis parameters for LD, MD, and Vehicle Control groups in the 4-week rat study with MDI (HFA) formulation.

Draft Letter to the Sponsor: We have reviewed your submission of August 26, 1997. At this time, we have the following comments and recommendations; some of these (1-4) have been conveyed to you during our meeting on September 17, 1997:



b(5)

Satish C. Tripathi, Ph.D.
Pharmacology/Toxicology Reviewer

Original IND
C.C. HFD-570/Division File
HFD-570/Joseph Sun, Team Leader, Pharmacology/Toxicology
HFD-570/Richard Nicklas, Medical Reviewer
HFD-570/Lindsay Cobbs, Project Manager
HFD-570/Satish Tripathi, Pharmacology/Toxicology Reviewer

ATTACHMENT 4.

**APPEARS THIS WAY
ON ORIGINAL**

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Review No. 4

IND Number: 53,391

Serial Number(s): N (RE)

Date(s) of Submission: Letter Date: December 15, 1997

Information to be Conveyed to Sponsor: Yes (X), No ()

Reviewer: Satish C. Tripathi, Ph.D.

Date Review Completed: March 20, 1998

Sponsor: Byk Gulden Lomborg Chemische Fabrik
GmbH, Postfach 10 03 10, 78403
Konstanz, Germany (Dr. Petra
Willersinn-Kern:
Tel: 011-49-7531-84-2837).

Sponsor (U.S. Representative): Altana Inc., 60 Baylis Road, Melville,
NY 11747 (Miss Virginia Carman:
516-454-7677 Extension 2091).

Manufacturer: _____ **b(4)**

Drug Name: Primary: Ciclesonide
Other Names: Byk Gulden B9207-015

Chemical Name: [11 β , 16 α (R)]-16, 17-[Cyclohexyl-
methylene) bis(oxy)-11-hydroxy-21-
(2-methyl-1-oxopropoxy) pregna-1, 4-
diene-3, 20-dione.

CAS Number: 141845-82-1

Molecular Weight and Formula: 540.7; C₃₂H₄₄O₇

Related INDs/NDAs/DMFs: DMF ~~XXXX~~ Toxicology testing of HFA-134a (MDI Propellant): XXXX **b(4)**

Class: Glucocorticoid Steroid.

Indication: Mild to moderate chronic asthma.

Clinical Formulation: White to off-white powder available as MDI that delivers —, 100, and 200 µg (ex valve) per puff. Other ingredients: — (w/w) propellant HFA-134a and — (w/w) ethanol.

Route of Administration: Inhalation (via MDI).

Previous Submission, Review Date and Reviewer:

Date of Submission	Reviewer	Review Date
05/23/97	Satish Tripathi	08/01/97
05/23/97	Satish Tripathi	09/05/97
08/26/97	Satish Tripathi	11/05/97

Studies Reviewed in this IND:

SAFETY PHARMACOLOGY
Rat: Effect on renal function and serum glucose after single i.p. administration; Vol. 3
TOXICOLOGY
Mice: 13-week oral dose ranging study; Vol. 18
Rat: Corticosterone levels in plasma following inhalation; Vol. 22
Dog: Draft Protocol: 13-wk inhalation toxicity with MDI (HFA) formulation; Vol. A
Toxicokinetics: Sprague Dawley Rat: 6 month toxicity study with DPI formulation; Vol. 7
Toxicokinetics: Sprague Dawley Rat: 4 week toxicity study with DPI formulation; Vol. 7
Toxicokinetics: Wistar Rat: 4 week toxicity study with MDI (HFA) formulation; Vol. 7
Toxicokinetics: Dog: 4 week toxicity study with MDI (HFA) formulation; Vol. 8
Validation of analytical procedures for toxicokinetics; Vol. 9
CARCINOGENICITY
Rat: Protocol of ongoing 24-month inhalation toxicity study; Vol. A
Mice: Protocol of planned 24-month oral toxicity study; Vol. A
RESPONSE TO FDA's COMMENTS; VOL. A

Note: Portions of this review were excerpted directly from the sponsor's submission.

Studies Previously Reviewed: Following studies were also submitted previously. See IND Reviews (No. 1 to 3) of Submissions of 05/23/97 and 08/26/97:

PHARMACOLOGY
Pharmacodynamics <i>in vivo</i> and <i>in vitro</i> ; Safety Pharmacology.
ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION
Absorption, distribution, metabolism in rats and dogs.
TOXICOLOGY
<ol style="list-style-type: none"> 1. Mice: Acute Toxicity (i.p.) 2. Mice: Acute Toxicity (p.o.). 3. Rat: Acute Toxicity (i.p.). 4. Rat: Acute Toxicity (p.o.). 5. Rat: 4-wk Inhalation Toxicity with Dry Powder Formulation. 6. Rat: 4-wk Dose Ranging Inhalation Toxicity with Metered-dose HFA-formulation. 7. Rat: 4-wk Inhalation Toxicity (MDI-HFA Formulation). 8. Rat: 26-wk Inhalation Toxicity with Dry Powder Formulation. 9. Dog: 4-wk Inhalation Toxicity with Dry Powder Formulation. 10. Dog: 52-wk Inhalation Toxicity with Dry Powder Formulation. 11. Dog: 4-wk Inhalation Toxicity with Metered-dose CFC-formulation. 12. Dog: 26-wk Inhalation Toxicity with Metered-dose CFC-formulation. 13. Dog: 4-wk Inhalation Toxicity (MDI-HFA Formulation). 14. Mice: 13-wk Oral Toxicity. 15. Rat: 4-wk Oral Toxicity. 16. Rat: 26-wk Oral Toxicity. 17. Dog: 4-wk Oral Toxicity. 18. Rat: 4-wk Subcutaneous Toxicity. 19. Rat: 26-wk Subcutaneous Toxicity. 20. Dog: 2-wk Intravenous Toxicity.
REPRODUCTIVE TOXICITY
<ol style="list-style-type: none"> 1. Rat: Segment II. 2. Rabbit: Segment II.

GENETIC TOXICITY
<i>In Vitro</i> tests: <ol style="list-style-type: none">1. Bacterial Reverse Mutation (Ames) test.2. Chromosomal aberration in human lymphocytes.3. HPRT test (V79 cells).4. Micronucleus test with V79 cells.
<i>In Vivo</i> tests: <ol style="list-style-type: none">1. Mouse micronucleus tests.
SPECIAL TOXICITY
<ol style="list-style-type: none">1. Guinea Pig: Skin sensitization study.2. Dog: Hemolytic potential following short-term intravenous administration.3. Guinea Pig: Primary irritation after single dose epicutaenous administration.4. Rabbit: Local Toxicity after a single intravenous, paravenous, or intraarterial administration.5. <i>In Vitro</i> Erythrocyte Stability test with rat, dog, and human blood.

Studies Not Reviewed: In the following study, only drugs other than Ciclesonide (Budesonide and Dexamethasone) were tested and, therefore, a review is not needed:

GENETIC TOXICITY

SAFETY PHARMACOLOGY

Rat: Effect on renal function and serum glucose after single i.p. administration

Byk Gulden 37/96; 18 April, 1997; Vol. 3

Administration of a single dose of 0, 0.1, 1.0 or 10.0 mg/kg of R and S Epimers of Ciclesonide to rats via i.p. route resulted in no toxicologically significant treatment-related effects on urinary volume, pH, osmolarity, and levels of electrolytes and on levels of serum glucose and electrolyte.

TOXICOKINETICS

A summary of all toxicokinetic data included in the submission is presented in Table 2. When Ciclesonide was administered to Sprague Dawley rats as DPI formulation, there was no accumulation of the drug (AUC) over a duration up to 6 months. In Wistar rats, when administered via MDI (HFA formulation), the accumulation of the drug (AUC) could not be determined due to lack of data. In addition, increase in the exposure (AUC) was less than proportional to increase in dose. In dogs, there was no accumulation (AUC) seen when the drug was delivered via MDI (HFA) formulation over a period of 1 month. However, with DPI formulation, there was some accumulation of the drug (AUC) seen during an exposure period from 3 months to 12 months. In dogs, increase in exposure (AUC) was proportional to increase in dose for MDI (HFA) formulation over a period of 1 month while, increase in exposure (AUC) was supraproportional to increase in dose when the DPI formulation of the drug was administered for 1 year. The exposure of the drug (AUC) was slightly higher in dogs than that in rats. The exposure of the drug (AUC) via MDI (HFA) formulation was comparable to that via DPI formulation in both rats as well as dogs, based on the 4-week studies.

APPEARS THIS WAY ON ORIGINAL

Table 2. Toxicokinetics of Ciclesonide

Parameters	Rat		Dog	
	MDI (HFA) (Wistar)	DPI (SD)	MDI (HFA)	DPI
Low Dose ($\mu\text{g}/\text{kg}/\text{day}$)	18	15	19	18
B9207-015 in inhaled air ($\mu\text{g}/\text{l}$)	1	1	2	2
AUC ($\mu\text{g}/\text{l}\cdot\text{h}$)				
Day 1			1.37	(2.06) ^x
Week 4	n.a.	n.a.	1.66	
C _{max} ($\mu\text{g}/\text{l}$)				
Day 1			0.69	(0.63) ^x
Week 4	n.a.	0.49	0.74	
AUC ($\mu\text{g}/\text{l}\cdot\text{h}$)				
Day 1		n.a.		n.a.
Month 3		n.a.		1.65
Month 6		n.a.		2.12
Month 12		n.a.		1.97
C _{max} ($\mu\text{g}/\text{l}$)				
Day 1		n.a.		n.a.
Month 3		n.a.		0.43
Month 6		n.a.		0.53
Month 12		n.a.		0.48
Middle Dose ($\mu\text{g}/\text{kg}/\text{day}$)	53	49	61	47
B9207-015 in inhaled air ($\mu\text{g}/\text{l}$)	3	3	7	6
AUC ($\mu\text{g}/\text{l}\cdot\text{h}$)				
Day 1			4.29	(4.89) ^x
Week 4	3.21 ³	2.02 ¹	5.07	
C _{max} ($\mu\text{g}/\text{l}$)				
Day 1			1.83	(1.43) ^x
Week 4	1.16 ³	1.20	1.83	
AUC ($\mu\text{g}/\text{l}\cdot\text{h}$)				
Day 1		2.71 ²		n.a.
Month 3		2.89 ²		4.17
Month 6		2.89 ²		5.19
Month 12				5.29
C _{max} ($\mu\text{g}/\text{l}$)				
Day 1		1.32		n.a.
Month 3		1.44		1.08
Month 6		1.70		1.40
Month 12				1.27
High Dose ($\mu\text{g}/\text{kg}/\text{day}$)	164	154	118	92
B9207-015 in inhaled air ($\mu\text{g}/\text{l}$)	10	10	15	12
AUC ($\mu\text{g}/\text{l}\cdot\text{h}$)				
Day 1			11.12	(17.18) ^x
Week 4	7.39 ³	5.65 ¹	10.33	
C _{max} ($\mu\text{g}/\text{l}$)				
Day 1			4.51	(3.00) ^x
Week 4	3.10 ³	3.55	4.07	
AUC ($\mu\text{g}/\text{l}\cdot\text{h}$)				
Day 1		8.21 ²		n.a.
Month 3		10.56 ²		5.64
Month 6		6.21 ²		7.60
Month 12				8.93
C _{max} ($\mu\text{g}/\text{l}$)				
Day 1		3.90		n.a.
Month 3		4.42		1.29
Month 6		2.97		1.84
Month 12				2.20

AUC is given as:

single dose 0 - inf h
 steady state 0 - 24 h
 exceptions: ¹ 0 - 4 h
² 0 - 5 h
³ 0 - 6 h

Remarks:

* no formal GLP during animal study

na = Not Ascertained

Validation of analytical procedures for toxicokinetics**b(4)**

The drug plasma levels were determined by solid phase extraction and liquid chromatography with tandem mass spectrometry. The lowest limit of detection was 25 pg/mL.

Rat: Corticosterone levels in plasma following inhalation

Byk Gulden Report 189E/97; Vol. 22

In order to study the influence of Ciclesonide on adrenal function in rats, plasma samples (n=5/Sex) from previously completed studies with DPI or MDI formulation of the drug (28-day, DPI: 94/1; 6-month, DPI: 94/5; 1-month, MDI: 96/11) were analyzed for determining levels of corticosterone. A summary of results are as follows:

Sprague-Dawley Rats: 28-day, DPI: Study No. 94/1: Treatment resulted in decreased levels of corticosterone (σ : 0.15 mg/kg/day: 45%; ♀ : 0.015 mg/kg/day: 25%; 0.05 mg/kg/day: 74%; 0.15 mg/kg/day: 84%).

Sprague-Dawley Rats: 6-month, DPI: Study No. 94/5: No toxicologically significant treatment-related effects were seen at 0.15 mg/kg/day.

Wistar Rats: 1-month, MDI: Study No. 96/11: No toxicologically significant treatment-related effects were seen at 0.15 mg/kg/day.

TOXICOLOGY

Mice: 13-week oral dose ranging study
Byk Gulden Study 20/97; 01 July, 1997; Vol. 18

Study Dates: August 21, 1996 to July 01, 1997

Testing Lab: Byk Gulden Institute of Pathology and Toxicology

Test Article: High dose solution was prepared by dissolving 22.5 mg of Ciclesonide in 50 mL of PEG 400; Low dose was prepared by diluting this solution.

GLP: Signed GLP Statement was not included.

METHODS

Species/Strain: Mouse B6C3F1

Animals: 30/Sex; 10/Sex/group

Route: Oral with a gastric canula

Dosage: 0 (Vehicle Control); 0.9 mg/kg/day (LD); 1.8 mg/kg/day (HD). Dosing Volume: 4 mL/kg.

Duration of Exposure: 13 weeks

Clinical Observations: Daily

Body Weights: Day -1, 2x/wk until day 31, 1x/wk until sacrifice

Food Consumption: Day -1, 2x/wk until day 31, 1x/wk until sacrifice

Ophthalmoscopy: Not conducted

Hematology: End of study

Clinical Chemistry: Not Conducted

Urinalysis: Not Conducted

Drug Levels: Not determined

Organ Weights: Not determined.

Gross- and Histopathology: Complete battery of histopathology of organs was performed.

RESULTS

Mortality: The sponsor stated that deaths in Control (♂: 4/10; ♀: 4/10) and LD (♂: 3/10) groups occurred on Day 19 due to a technical mistake i.e. the animals received 10 times the required dose on Day 19. It is not clear whether the death of 8 animals of control group was due to receiving 10-fold of the concentration of the vehicle. Two females of LD group died due to administration of the Test article into the lung.

Clinical Signs: No toxicologically significant treatment-related effects.

Body Weights: Treatment resulted in 43% decrease in body weight gains in both dose groups.

Food Consumption: No toxicologically significant treatment-related effects.

Hematology: No toxicologically significant treatment-related effects.

Gross Pathology: No toxicologically significant treatment-related effects.

Histopathology: The following changes were significant:

Table 1. Histopathologic Findings in a 13-wk Mouse Oral Dose Ranging Study

Finding	Vehicle Control	LD	HD
Adrenal gland: Increased x-zone vacuolation: ♀:	5/9	8/10	10/10
A-cell hyperplasia: ♀:	5/9	8/10	10/10
Liver: Centrilobular hypertrophy: ♂:	2/8		6/10
Increased Glycogen storage: ♂:			3/10
♀:		4/10	2/10
Thymus: Cortical atrophy: ♂:		7/9	8/10
♀:		5/10	5/10
Cysts: ♀:		1/10	2/10
Lung: Hemorrhage: ♀:		1/10	2/10
Ovary: Atrophy:		2/10	0/10
Karyorrhexis in corpora lutea:	1/6	3/10	4/10
Uterus: Glandular ectasia :			2/10
Mucosal atrophy:			1/10

In the absence of signed GLP statement and unavailability of data on ophthalmoscopy, clinical chemistry, urinalysis, organ weights, and drug plasma levels, this study cannot be considered valid for safety determination. Based on decreased (43%) bodyweight gains in both dose groups, it can be concluded that the MTD was less than 0.9 mg/kg/day.

CARCINOGENICITY

Mice: Protocol of planned 24-month oral (gavage) toxicity study

Byk Gulden Study; Vol. A

Dose selection [0 (Vehicle Control), 0.15, 0.45, and 1.35 mg/kg/day] for this planned study is based on data from 2 non-GLP dose ranging 13-week oral (gavage) toxicity studies. In one of these 13-week mouse study (see page 8-9 of this review), doses of 0 (Vehicle Control), 0.9, and 1.8 mg/kg/day were used. Based on decreased (43%) bodyweight gains, it can be concluded that the MTD in this study was less than 0.9 mg/kg/day. In the second 13-week mouse dose ranging study (See pages 6-7 of Review #2), doses of 0 (Vehicle Control), 0.05, 0.15-0.9 (due to no bodyweight gain by the end of week 4, the middle dose i.e. 0.15 mg/kg/day was increased to 0.9 mg/kg/day for remainder 9 weeks of the study), and 0.45 mg/kg/day were tested. Based on 12% decrease in bodyweight gains in females at 0.05 mg/kg/day, the MTD (for females) was 0.05 mg/kg/day. Although treatment resulted in no effect on bodyweight gain in males at any dose, incidence of follicular atrophy of spleen in 8 out of 10 animals was reported at 0.9 mg/kg/day. The HD (1.35 mg/kg/day) seems to exceed the MTD.

This Reviewer had conversation with Ms. Virginia Carman of Altana, Inc. (U.S. Representative of Byk Gulden) over the telephone (February 23, 1998) and asked her whether Byk Gulden would like to receive Agency input regarding appropriateness of dose selection for carcinogenicity study in mice. In addition, it was also pointed out that Agency input could be provided only after concurrence with CDER's Carcinogenicity Assessment Committee. On March 16, 1998, Ms. Carman advised that Byk Gulden would like to receive Agency opinion on dose selection for carcinogenicity study in mice.

Rat: Protocol of ongoing 24-month inhalation toxicity study

Byk Gulden Study; Vol. A

This study is being conducted in Wistar rats while dose selection is based on 1 and 6 month studies in Sprague-Dawley rats (per sponsor). The sponsor indicated that mammary tumor incidence in Sprague-Dawley rats is up to 90% in a long-term study which may cause difficulty in keeping animals with mammary gland tumors in inhalation tubes.

The doses used in the 1 and 6 month studies with DPI formulation were about 0.015,

0.05, and 0.15 mg/kg/day. The NOAEL in the 1 month study was 0.05 mg/kg/day while the NOAEL in the 6 month study was 0.015 mg/kg/day. Since a typical 3-month dose ranging study in rats was not conducted, 6-month study can be used for dose selection for carcinogenicity study. In the 6-month rat study, treatment resulted in decreased body weight in both sexes (σ : 15% at 0.15 mg/kg/day; ♀ : 10% at 0.05 mg/kg/day. In addition, there were incidences of multifocal interstitial mononuclear cell infiltration (12/20) at 0.05 mg/kg/day in males and increased glandular development of mammary gland (9/20) in females at 0.05 mg/kg/day. Based on these effects, the MTD in the 6-month study with DPI formulation was somewhere between 0.015 and 0.05 mg/kg/day. The doses selected for carcinogenicity study are 0 (Vehicle Control), 0.015, 0.0375, and 0.094 mg/kg/day. The middle dose (0.0375 mg/kg/day) seems to be close to MTD. The high dose (0.094 mg/kg/day) seems to exceed the MTD. The sponsor did not ask for Agency input regarding dose selection and the study is already in progress. The appropriateness of dose selection and validity of the study will be reviewed upon submission.

APPEARS THIS WAY ON ORIGINAL

RESPONSE TO FDA's COMMENTS; VOL. A***NOAEL in 6-month Inhalation Toxicity Study in Rats (DPI formulation):***

A NOAEL dose in a 6-month inhalation toxicity study in rats could not be established due to the incidence of multifocal histiocytosis in the lungs. As shown below (scoring by Pathologist #1), there was dose dependent increase in the incidence of alveolar histiocytosis of 'slight' grade in males:

PATHOLOGIST #1: INCIDENCE OF ALVEOLAR HISTIOCYTOSIS

Finding	C	LD	MD	HD	C Recovery	HD Recovery
Focal/multifocal histio. Slight						
♂	3	6	8	10	0	1
♀	0	6	2	3	1	1
Very slight						
♂	13	14	10	9	10	7
♀	17	12	18	15	8	7
Total (slight+v. slight)						
♂	16	20	18	19	10	8
♀	17	18	20	19	9	8

In the Volume A of Submission dated December 15, 1997, the sponsor provided data obtained from peer review of histopathologic slides from the 6-month rat study.

Incidences of multifocal histiocytosis in the lungs scored by Pathologist #2 are as follows:

PATHOLOGIST #2: INCIDENCE OF ALVEOLAR HISTIOCYTOSIS

Finding	C	LD	MD	HD	C Recovery	HD Recovery
Focal/multifocal histio. Slight						
♂	2	3	1	3	0	0
♀	0	5	1	2	0	1
Very slight						
♂	6	4	8	5	3	1
♀	3	8	4	5	0	1
Total (slight+v. slight)						
♂	8	7	9	8	3	1
♀	3	13	5	7	0	2

Evaluation by peer pathologist showed alveolar histiocytosis of 'slight' grade not to be significant. The sponsor indicated that difference in data on evaluation of histopathologic slides by two pathologists was due to the fact that the previous

pathologist recorded also the presence of normal-appearing alveolar macrophages as 'alveolar histiocytosis.' Due to excessive pharmacologic steroid effects seen by histopathologic changes (typical steroid effects) at 0.05 mg/kg/day in mammary gland (glandular development) and lungs (multifocal interstitial mononuclear cell infiltration and bronchus-associated lymphoid tissue atrophy) and changes at 0.166 mg/kg/day in thymus (lymphoid depletion of cortex), lymph nodes (mesenteric lymph node depletion), and lungs (multifocal interstitial mononuclear cell infiltration and bronchus-associated lymphoid tissue atrophy), the lowest dose (0.0165 mg/kg/day) should be regarded as the NOAEL for this study.

NOAEL in 12-month Inhalation Toxicity Study in Dogs (DPI formulation):

In a 12-month inhalation toxicity study in dogs with DPI formulation, the NOAEL could not be established due to the findings of chondrosis and osteofibrosis of turbinalia in the nasal cavity. Since route of administration of the drug in humans is oral inhalation, we have no safety concern if these effects are not due to its systemic effect. In a meeting with the sponsor (September 17, 1997), it was pointed out that negative finding on the incidence of chondrosis and osteofibrosis of turbinalia, if confirmed by systemic route, would suggest that these findings in the inhalation study are due to local effect of the drug and not due to systemic effect. The sponsor had conducted a 12-month oral study to confirm this. We have now been informed that a report of that study will not be available until August, 1998. Thus, the nasal cavity findings in dogs remain unresolved. Thus, in the face of NOAEL not being established in the 12-month inhalation toxicity in dogs (DPI formulation), it is not certain that a 3 month inhalation toxicity study in dogs with MDI (HFA) formulation would be adequate.

6-MONTH BRIDGING STUDY

The sponsor was recommended to conduct a six month study in rats with MDI (HFA) formulation if NOAEL cannot be established in previously conducted 6-month rat study with DPI formulation and if data from a 12-month oral toxicity study in dogs could show that the nasal cavity changes in the 12-month dog study are due to local (and not systemic) effect.

The FDA, in a meeting on September 17, 1997, had indicated that if NOAELs in 6-month rat and 12-month dog studies with DPI formulation can be established then, a 3-month study in dogs with MDI (HFA) formulation may be adequate. During the same meeting, the sponsor had indicated that data from 12-month oral toxicity study in dogs were available. In the present submission (December 15, 1997), the sponsor

indicated that the final report of 12-month dog oral toxicity study would be available in

January, 1998. We have now been informed that the final report of this study will not be available until August, 1998 although we agree with the sponsor that a NOAEL was established in the 6-month study in rats. In the absence of such crucial data, a decision on bridging study requirement cannot be reached.

Dog: Draft Protocol: 13-wk inhalation toxicity with MDI (HFA) formulation

Since NOAEL in 12-month dog inhalation toxicity study (DPI formulation) is not established and data from 12-month dog oral toxicity study are not available, the 13-wk inhalation (MDI-HFA formulation) toxicity study in dog will not serve the purpose of bridging to 12-month dog study (DPI formulation). However, if data from 12-month dog oral toxicity study do not show nasal cavity changes then a 13-wk inhalation (MDI-HFA formulation) toxicity study in dogs will be sufficient.

The sponsor proposed to administer 0 (vehicle control), 0.0075, 0.052, and 0.09 mg/kg/day of the drug to dogs via inhalation (MDI-HFA formulation) for a period of 13-weeks. In a 4-week inhalation toxicity study with the same formulation of the drug (See Review #3; Submission of 08/26/97), 0.061 mg/kg/day was the NOAEL while at 0.118 mg/kg/day, there were exaggerated pharmacologic effects as shown by histopathologic changes (cortical atrophy of thymus, loss of secondary follicles in spleen, atrophy of Zona fasciculata in adrenals, and loss of secondary follicles in lymph nodes). Based on these findings at 4-week, the dose selection for this 13-week study is acceptable.

APPEARS THIS WAY ON ORIGINAL

OVERALL SUMMARY AND EVALUATION

Safety Pharmacology: In rats, single i.p. administration of up to 10 mg/kg of Ciclesonide resulted in no significant effect on urinary parameters and levels of serum glucose and electrolyte.

Toxicokinetics: The exposure of the drug (AUC) was higher in dogs than that in rats. The exposure of the drug (AUC) via MDI (HFA) formulation was comparable to that via DPI formulation in both rats as well as dogs. In rats, there was no accumulation of the drug and increase in exposure (AUC) was \leq proportional to dose. In dogs, increase in exposure (AUC) was proportional to increase in dose for MDI (HFA) formulation over a period of 1 month while, increase in exposure (AUC) was supraproportional to increase in dose when the DPI formulation of the drug was administered for 1 year.

In Sprague Dawley rats, treatment with the drug (DPI formulation) for 1 month at a dose \leq 0.015 mg/kg/day resulted in the suppression of corticosterone levels. However, at the same dose, it did not produce any suppression of cortisone in Wistar rats neither in the one-month nor in the six-month study. Data suggested that its effect on cortisone was inconsistent.

Toxicology: In mice, administration of 0.9 and 1.8 mg/kg/day of the drug for 3 months via oral route (gavage) resulted in decreased bodyweight gains at both doses. Histopathologic changes consisted of centrilobular hypertrophy and increased glycogen storage in liver and cortical atrophy in thymus. Changes that occurred in females only consisted of incidence of cysts in thymus; increased x-zone vacuolation and A-cell hyperplasia in adrenal glands; hemorrhage of lungs; atrophy of ovary and karyorrhexis in corpora lutea; and glandular ectasia and mucosal atrophy of the uterus. All histopathologic changes except for those in the uterus were seen at 0.9 mg/kg/day. The target organs of toxicity were thymus and liver in both sexes and adrenal gland, lungs, ovary, and uterus in females. The MTD was less than 0.9 mg/kg/day.

In another 13-wk dose ranging oral (gavage) toxicity study in mice (See pages 6-7 of Review #2 of Submission dated May 23, 1997), treatment with 0.05, 0.15-0.9, and 0.45 mg/kg/day of the drug resulted in decreased bodyweight gains at 0.45 mg/kg/day in females and splenic follicular atrophy in males at 0.9 mg/kg/day implying that high dose (1.35 mg/kg/day) may exceed the MTD in the proposed mouse carcinogenicity study.

Carcinogenicity: The sponsor had not asked for Agency input to the selection of doses for carcinogenicity studies in mice and rats. The sponsor has begun the rat study in April,

1997 and is planning to start mouse study in April, 1998. A review of the dose regimens suggests the employment of the MTD in both studies. In addition, the highest dose may be exceeding the MTD. The strain of rats used for carcinogenicity study is different from the strain used in the 6-month study with DPI formulation. Concurrence from the Executive CAC regarding dose selection and validity of the studies should be obtained upon the submission of the data.

The sponsor was contacted over the telephone (02/20/98; 3/16/98; 3/20/98) to determine whether or not they would like to receive Agency input regarding appropriateness of dose selection and study design for the ongoing carcinogenicity study in rats and proposed carcinogenicity study in mice.

Comments on Draft Protocol for proposed 13-wk inhalation toxicity in dogs with MDI (HFA) formulation:

Since NOAEL in 12-month dog inhalation toxicity study (DPI formulation) is not established and data from 12-month dog oral toxicity study are not available, the 13-wk inhalation toxicity study in dog will serve the purpose of bridging to 12-month dog study (DPI formulation) only if such information is available and local effects of such findings are confirmed by the data.

The sponsor proposed to administer 0 (vehicle control), 0.0075, 0.052, and 0.09 mg/kg/day of the drug to dogs via inhalation (MDI-HFA formulation) for a period of 13-weeks. Based on findings from a 4-week inhalation toxicity study with the same formulation of the drug (See Review #3; Submission of 08/26/97), the dose selection for this study is acceptable.

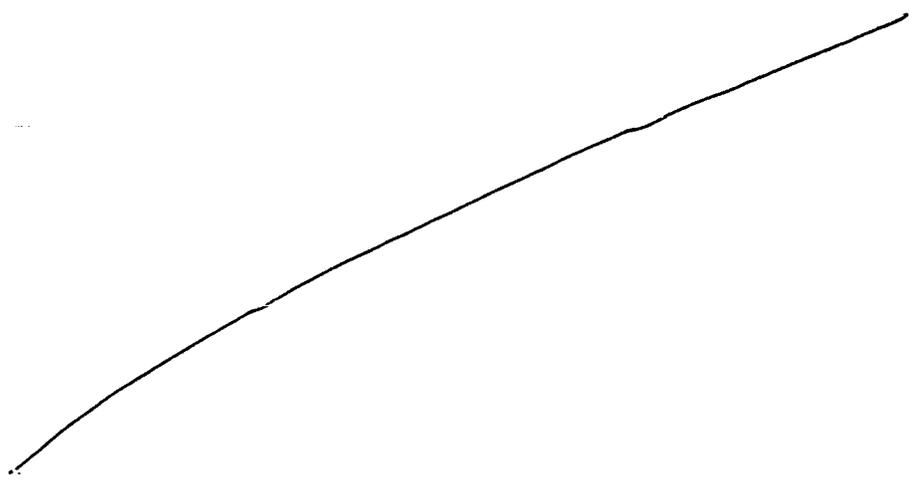
RECOMMENDATION

Present Review: The protocol of 3 months bridging study in dogs is acceptable. However, due to the lack of clear NOAEL in 12-month inhalation toxicity study in dogs with DPI formulation and unavailability of report of 12-month oral toxicity study in dogs, it is not certain that 3-month inhalation (MDI-HFA formulation) toxicity study in dogs would be adequate to bridge from DPI to MDI formulation. Per teleconferences on 02/20/98, 3/16/98, and 3/20/98, the sponsor will inform the Agency as to whether or not concurrence from the Executive CAC will be obtained regarding dose selection and design of the ongoing study for carcinogenicity assay in rats and proposed carcinogenicity assay in mice. The sponsor should provide any deviation from GLP for any studies that did not comply with the GLP.

Therefore, concurrence of the Executive CAC should be obtained regarding dose selection for this study upon receiving their official correspondence of such request.

Review No. 3 (Submission of August 26, 1997): Rationale should be provided for not determining weights of all organs and urinalysis parameters for LD, MD, and Vehicle Control groups in the 4-week rat study with MDI (HFA) formulation.

Draft Letter to the Sponsor: We have reviewed your submissions of August 26, 1997 and November 25, 1997. At this time, we have the following comments and recommendations:



b(5)

Satish C. Tripathi, Ph.D.
Pharmacology/Toxicology Reviewer

Original IND

- C.C. HFD-570/Division File
- HFD-570/Joseph Sun, Team Leader, Pharmacology/Toxicology
- HFD-570/Richard Nicklas, Medical Reviewer
- HFD-570/Lindsay Cobbs, Project Manager
- HFD-570/Satish Tripathi, Pharmacology/Toxicology Reviewer

ATTACHMENT 5.

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

KEY WORDS: 12-month dog oral toxicology, nasal turbinates, histology, re-evaluation, historical controls

Reviewer Name: W. Mark Vogel, Ph.D.

Division Name: Division of Pulmonary Drug Products

HFD#: HFD-570

Review Completion Date: March 1, 1999

Review Number: Review # 6

IND Number: IND 53,391

Serial Number: N018

Submission Date: 08 September 1998

Submission Type: Toxicology amendment

Information to Sponsor: Yes (✓), No ()

Sponsor or Agent: *Sponsor:* Byk Gulden, Konstanz, Germany
Agent: Altana Inc., Melville, New York

Manufacturer: _____

Drug: *Code Name:* B9207-015 b(4)
Generic Name: Ciclesonide
Proprietary Name: Not determined
Chemical Name: [11β, 16α(R)]-16, 17- [cyclohexylmethylene] bis(oxy)-11-hydroxy-21-(2-methyl-1-oxopropoxy)pregna-1, 4-diene-3, 20-dione
CAS Registry Number: 141845-82-1
Molecular Formula: C₃₂H₄₄O₇ *Molecular Weight:* 540.7

Relevant INDs/NDAs/DMFs:

DMF: toxicity testing of HFA-134a,

Drug Class: Glucocorticoid Steroid

Indication: Asthma

Clinical Formulation:

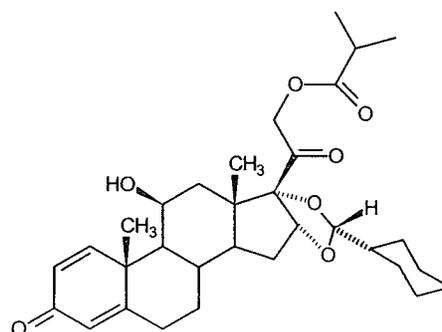
MDI with HFA-134a propellant & ethanol

Route of Administration: Oral Inhalation

Previous Reviews, Dates and Reviewers:

No. Submission:	Submitted	Reviewer	Reviewed
1 Original IND	02 Jun 97	S.C. Tripathi	01 Aug 97
2 Original IND (addendum review)	02 Jun 97	S.C. Tripathi	05 Sep 97
3 Original IND (addendum review) and response to previous comments	02 Jun 97 26 Aug 97	S.C. Tripathi	05 Nov 97
4 Inhalation TK, safety pharm, 13 wk dog & mouse	15 Dec 97	S.C. Tripathi	20 Mar 98
5 Mouse and rat carcinogenicity protocols	14 May 98	W.M Vogel	08 Jul 98

Structure:



b(4)

Proposed clinical protocol or use: Phase-1 and phase-2 studies up to 3 months duration at doses up to 1600 µg/day have been proposed. The sponsor has been advised that adequate bridging studies (with the HFA formulation to the previous chronic rat and dog studies with the DPI formulation) are needed before initiating long term clinical safety studies greater than 3 months duration.

Note: Some material may be taken directly from sponsor's submission.

Introduction/Drug History: Pharmacodynamics, safety pharmacology, pharmacokinetics, acute toxicity, inhalation toxicity, developmental toxicity, genetic toxicity, and skin sensitization studies were reviewed in the original IND pharm/tox review. The second pharm/tox review covered mouse, rat and dog toxicity studies by oral, s.c., and i.v. routes, and special toxicity studies (hemolytic potential, cutaneous and vascular irritation studies). Rat and dog 4-week inhalation studies and a draft dog 13-week protocol were addressed in the third pharm/tox review. Mouse and rat carcinogenicity protocols, inhalation toxicokinetics, renal safety pharmacology, and 13-week dog and mouse oral toxicity studies were covered in review #4. The fifth review was a briefing package for the executive Carcinogenicity Assessment Committee to consider concurrence with proposed rodent carcinogenicity protocols.

Clinical studies under this IND are approved for up to 3-months duration based on preclinical toxicology profile (typical steroid toxicity) and previous European clinical experience (800 µg/day for 3 months). Nasal cavity changes (osteofibrosis, chondrosis and osseous disorganization) were observed in a 12-month dog nose-only inhalation study. The sponsor asserted that the nasal findings represented common "background noise" but did not present historical data to support that contention. The Division recommended that the sponsor conduct a 12-month oral dog study at similar plasma ciclesonide concentrations to support their assertion that nasal osteofibrosis is due to local nasal inhalation and not relevant to human clinical oral inhalation. The sponsor notes in the 14 May 1998 submission that the in life part of the study was concluded in April 1998. An **unaudited draft report** of that study is in the present submission (08 Sep 98); histology is complete only for target organs. Background data on ciclesonide and two other drugs with a blinded re-reading of nasal cavity histological slides was presented to characterize the incidence of the nasal finding. Treatment related lung histiocytosis was observed in the 6-month rat dry powder inhalation toxicity study. The sponsor provided additional information that this finding was spurious (see review #4, 20 Mar 98). In a teleconference on 19 March 1998, the Division noted that Byk Gulden's explanation for the incidence of alveolar histiocytosis in the 6-month rat study is reasonable.

Studies Reviewed within this Submission:

Study	Company #	Vol / Pg
Histological evaluation of nasal turbinates from 5 studies	Discussion 117D/98 K1	1/5
Draft report 12-month oral dog toxicity study*	Report # 136/98	1/16

Studies Not Reviewed within this Submission: None

TOXICOLOGY

Histologic evaluation of the nasal turbinates- Comparison of 5 different dog studies.

Discussion # 117D/98 K1, Volume 1, page 05

Methods: This study was a re-evaluation of microscopic slides of the nasal turbinates from five different dog inhalation toxicity studies. The specific drugs and studies are identified in Table 1 on the following page. There is no indication that this re-reading was audited or carried out according to Good Laboratory Practices. The nasal turbinates were cut transversely on 3 different planes. Tissue samples were decalcified, embedded, and stained with either Hematoxylin-Eosin or Alcian Blue-PAS. The middle section was evaluated using a blind reading, in which the slides were coded and sorted randomly so that the pathologist had no knowledge of the study type or substance. The primary observations were the incidence of osteofibrosis and of trabecular thickening. "Trabecular thickening" referred to the finding of either osseous disorganization or chondrosis. A number of secondary histologic endpoints were noted, such as number of goblet cells and morphometric analysis of trabecular thickness. Individual line listings for nasal pathology were included for each animal. There were no obvious differences between males and females in the incidence of the various findings and the combined results are presented in this review.

Results: Results of the histologic examination for osteofibrosis and trabecular thickening (osseous disorganization + chondrosis) are summarized in Table 1 on the following page. There were a number of discrepancies in the incidence of these findings between the original and second reading. For example, no osteofibrosis was reported in control dogs in the original study but there were 2/8 animals with this finding in the re-reading. In the original study the incidence of osteofibrosis was 5/7 at the mid-dose but was only 2/7 in the re-evaluation. Additional discrepancies were apparent for the finding of trabecular thickening. Looking at the control groups it is obvious that there is a very wide variability in the incidence of these findings. For osteofibrosis, the incidence ranged from 0/8 up to 5/7. For trabecular thickening, the incidence ranged from 1/8 up to 4/8. For individual animals the severity of the finding was always graded as minimal or slight (scores of 1 or 2). Trabecular area assessed by morphometry in the 12-month ciclesonide study had a rough correspondence with the histologic finding of trabecular thickening. For 19 animals without a finding of trabecular thickening, pooled from all groups, the measured trabecular area was 18.7 ± 0.3 (SEM) $\times 10^7 \mu^2$; for 12 animals from all groups with a finding of trabecular thickening the measured area was $20.3 \pm 0.6 \times 10^7 \mu^2$, an increase of 8%. However, the morphometric measurement did not demonstrate any treatment related differences among groups. In controls, low-, mid-, and high-dose groups, respectively, trabecular thickness was 19.5, 19.8, 18.7, and $19.3 \times 10^7 \mu^2$. The incidence of osteofibrosis and trabecular thickening in the groups treated with the phosphodiesterase inhibitors showed similar wide inter-group variability without any obvious treatment related effects.

Table 1: Incidence of findings in the nasal turbinates from 5 different dog inhalation studies.

Osteoifibrosis	Study #	Dose Level 1		Dose Level 2		Dose Level 3		Dose Level 4						
		SS+	#	n	SS+	#	n	SS+	#	n				
12-mo ciclesonide DPI: (0, 18, 47,92 µg/kg)	original → re-read →	HD0356 "	---	0	8	---	4	8	---	5	7	---	7	8
			0.25	2	8	0.75	3	8	0.43	2	7	1.13	6	8
4-wk ciclesonide DPI (0, 15, 50, 100 µg/kg)		HD0293	0.00	0	8	0.00	0	8	0.00	0	8	0.25	1	8
4-wk ciclesonide HFA (0, 19, 61, 118 µg/kg)		HD0459	0.75	4	8	1.50	7	8	1.38	6	8	1.25	7	8
4-wk tolatentrine* DPI (0, doses not reported)		HD0254	0.88	5	8	0.50	2	8	0.13	1	8	0.38	2	8
4-wk roflumilast** DPI (0, dose not reported)		HD0442	1.43	5	7	---	---	---	---	---	---	1.00	3	5
all controls = 0.66 34%														
Trabecular thickening		Study #	Dose Level 1		Dose Level 2		Dose Level 3		Dose Level 4					
			SS	#	n	SS	#	n	SS	#	n			
12-mo ciclesonide DPI: (0, 18, 47,92 µg/kg)	original → re-read →	HD0356 "	---	1	8	---	7	8	---	7	8	---	8	8
			0.25	1	8	0.88	5	8	0.25	1	8	1.25	5	8
4-wk ciclesonide DPI (0, 15, 50, 100 µg/kg)		HD0254	0.63	4	8	0.88	4	8	0.38	2	8	0.50	3	8
4-wk ciclesonide HFA (0, 19, 61, 118 µg/kg)		HD0459	0.63	4	8	1.38	6	8	1.25	6	8	0.75	4	8
4-wk tolatentrine* DPI (0, doses not reported)		HD0293	0.25	1	8	0.25	1	8	0.00	0	8	0.63	3	8
4-wk roflumilast** DPI (0, dose not reported)		HD0442	1.00	4	8	---	---	---	---	---	---	0.25	2	8
all controls = 0.55 31%														

*PDE IV inhibitor; ** PDE III/IV inhibitor; †SS = average severity score (0 = normal, 1 = minimal, 2 = slight, 3 = moderate, 4 = severe)
indicates number of animals with finding; "n" indicates number of animals available for examination; males and females are combined.

Toxicity of B9207-015 in beagle dogs following oral administration for 12 months.

Research Report #136/98, Vol. C9.1, pg. 16

Study Dates: Initiated 20 March 1997; Draft report dated 1998*Testing Lab:* Not indicated.*Test Article:* Ciclesonide batch MG 225 C*GLP:* This draft report was not accompanied by a signed GLP statement.*QA Report:* Yes () No (✓)**Methods:**

Beagle dogs (males 9.0 months, 12.1 kg; females 9.2 months, 9.7 kg) were assigned to:

Dose ($\mu\text{g}/\text{kg}$)	0	5	30	200
No./sex/group main study	5	5	5	5
No./sex/group 4-wk recovery	0	0	0	2

Drug was administered as a suspension in PEG 400 in gelatinous capsules. The following observations were made:

Clinical signs timing of measurements not indicated

Body weight weight gains reported for days: 25, 88, 179, 361

Food intake timing of measurements not indicated

Ophthalmology timing of measurements not indicated

Physical exam body temperature, pulse rate and respiratory rate reported for weeks: -2, 25, and 52

Electrocardiogram reported for weeks: -2, -1, 13, 25, and 51 (timing of EKG relative to daily dosing not indicated)

Clinical pathology reported for weeks: -2, -1, 4, 13, 25, 52

Urinalysis reported for weeks: -2, 25, 52

Plasma Cortisol samples obtained but results not yet available

Plasma drug levels no details reported

Necropsy terminal

Histopathology only target tissues evaluated at present: adrenals, thymus, lymph nodes, spleen, liver, lung, nasal cavity.

Results: Tabular summaries of group data were presented; individual line listings were provided only for histology. Findings are summarized in Table 2, page 7.*Mortality:* None reported*Clinical Signs:* Summary states no treatment related effects were observed; no data were presented.*Body Weight:* A dose-related decrease in body weight gain was statistically significant for high dose females as shown in Table 2.*Food Intake:* Summary states no treatment related effects were observed; no data were presented.

Ophthalmoscopy: Summary states no treatment related effects were observed; no data were presented.

Physical Exam: No toxicologically significant treatment-related effects.

Electrocardiogram: No toxicologically significant treatment-related effects.

Hematology: No toxicologically significant treatment-related effects. Expected changes, such as decreased lymphocytes and increased neutrophils, were not observed.

Clinical Chemistry: No toxicologically significant treatment-related effects.

Urinalysis: No toxicologically significant treatment-related effects.

Plasma Cortisol: Results not yet available.

Organ Weights: Adrenal weight decreased at the high dose (24%↓ in males; 41%↓ in females). Spleen weight was not significantly decreased but variation was large. Thymus weight was not reported.

Gross Pathology: No toxicologically significant treatment-related effects.

Histopathology: Several expected glucocorticoid effects were observed. Adrenal cortical atrophy occurred at the high dose and in one mid-dose female. Atrophy of the thymus was observed only in males, particularly at the mid and high-dose with one occurrence at the low dose. Follicular atrophy of the spleen was observed in several treated groups with the greatest incidence at the high dose. Centrilobular hepatocyte hypertrophy was also seen in several treated groups with the greatest incidence at the high dose. Lung and nasal cavity were examined and no abnormalities were reported.

Toxicokinetics: No results presented.

Table 2: Results from 12-month Oral Dog Study

Dose (µg/kg) →	Males				females			
	0	5	30	200	0	5	30	200
Body weight gain (kg)	1.3 ±0.8	1.6 ±0.6	0.8 ±1.2	0.5 ±1.4	2.1 ±0.7	1.7 ±0.4	1.6 ±0.6	0.6 ±0.5
Range (kg)	0.6-2.3	0.8-2.2	-0.3-2.7	-0.9-3.4	1.4-3.2	1.2-2.1	0.5-2.2	0.0-1.3
Adrenal weight (g)	0.70 ±0.16	0.75 ±0.11	0.65 ±0.14	0.53 ±0.08	0.79 ±0.12	0.77 ±0.10	0.71 ±0.10	0.46 ±0.08
%Δ vs control		7.2%	-7.2%	-24%		-2.5%	-10.2%	-41%
Adrenal atrophy	0/5	0/5	0/5	4/5	0/5	0/5	1/5	1/5
Thymus atrophy	0/5	1/5	4/5	5/5	0/5	0/5	0/5	0/5
Spleen atrophy	1/5	2/5	0/5	5/5	0/5	3/5	4/5	4/5
Liver centrilobular hypertrophy	1/5	1/5	4/5	4/5	1/5	2/5	0/5	4/5

Highlighted cells indicate statistical significance vs control group

Key Study Findings: This is a draft report. Plasma cortisol and toxicokinetics are not yet available; histopathology was completed only for target organs. Dogs were treated

orally for 12-months with 5, 30 or 200 $\mu\text{g}/\text{kg}$ ciclesonide. The effects were relatively mild expected glucocorticoid effects. Body weight gain was decreased at the high dose (from 1.3 kg in controls to 0.5 kg in high-dose males; from 2.1 kg in controls to 0.6 kg in high-dose females). Expected glucocorticoid effects on hematology and clinical chemistry were not observed. Adrenal weight decreased at the high dose (24% \downarrow in males, 41% \downarrow in females); spleen weight was not significantly decreased; thymus weight was not reported. Microscopic changes were: adrenal cortical atrophy at the high dose, thymus atrophy in mid- and high-dose males, follicular atrophy in the spleen and centrilobular hypertrophy in the liver in several treated groups with highest incidence at the high dose. Examination of nasal cavity and lung revealed no treatment related effects. The NOAEL is 30 $\mu\text{g}/\text{kg}$, a dose that produced mild, tolerable, expected glucocorticoid effects.

OVERALL SUMMARY AND EVALUATION

Re-evaluation & Background Data on Nasal Histology: The re-evaluation of nasal trabecular histology indicates that the findings of osteofibrosis and of trabecular thickening, are background findings with a quite variable incidence. (Trabecular thickening includes either chondrosis or osseous disorganization.) The incidence of osteofibrosis in individual control groups ranged from 0-71% (34% overall) and the incidence of trabecular thickening ranged from 12-50% (31% overall). The variability in the incidence of these findings from study to study and between original observations and re-reading suggests that there is considerable subjectivity in the definition of these findings and/or marked heterogeneity in the spatial distribution of the finding. Another point consistent with this interpretation arises from the re-evaluation of the 4-week ciclesonide HFA study (HD0459). In the re-evaluation, the incidence and mean severity scores for osteofibrosis in all treated groups of that study were equal to or greater than in the high-dose group from the 12-month inhalation study; yet there was no mention of the finding in the pharm/tox review of the original 4-week study.

The variability in these findings makes it difficult to distinguish a NOAEL. The mid-dose of 47 $\mu\text{g}/\text{kg}$ in the 12-month ciclesonide DPI study appears to be a NOAEL for nasal cavity findings (dose level 3 in Table 1). The incidence of osteofibrosis and trabecular thickening at the high dose are greater than in any of the control groups. The NOAEL of 47 $\mu\text{g}/\text{kg}$ offers only a small safety margin over the maximum proposed clinical dose (1600 $\mu\text{g}/50 \text{ kg} = 32 \mu\text{g}/\text{kg}$). However, even if there is a real increase in the incidence of these findings at the high dose, the high background incidence tends to minimize the toxicological significance of such an increase. Because of the high and variable background incidence, these findings would be a safety concern only if they occurred with increased severity. The findings were not of increased-severity even at the high dose. Osteofibrosis and trabecular thickening were never graded more than minimal or slight in any group. In fact, at the high dose, the average severity score for osteofibrosis of 1.13 (1 = minimal, 2 = slight) was less than that of 1.43 for the highest control group. Similarly, the average

severity score of 1.25 for trabecular thickening at the high dose is only slightly greater than the score of 1.0 for the highest control group. This is consistent with the inability to detect increased trabecular thickening at the high dose by morphometry. In the absence of increased severity of these findings the observed increased incidence of osteofibrosis and trabecular thickening should not be considered dose-limiting toxicities.

One-year Oral Dog Toxicity Study: This draft report revealed relatively mild expected glucocorticoid effects consisting of decreased body weight gain, adrenal suppression manifested as decreased adrenal weight and microscopic cortical atrophy, mild lymphoid atrophy of spleen and thymus, and centrilobular hepatic hypertrophy without a significant change in liver weight. No effects were observed on the lung or nasal cavity. Specifically, there was no incidence in any group of the osteofibrosis, and trabecular thickening that was the subject of the histological re-evaluation of the inhalation studies. This could be further evidence of the sporadic and subjective nature of this finding or might mean the findings in the inhalation studies resulted from the inhalation procedure rather than drug treatment. The NOAEL was 30 $\mu\text{g}/\text{kg}$. Because there was no effect on the nasal cavity in this oral study, the sponsor argues that the nasal findings at the high dose in the dog 12-month dry powder inhalation study were due to a local effect of nasal inhalation and deposition. It is not possible to compare systemic exposure in the two studies because plasma drug levels have not yet been reported for the oral study. It seems likely that systemic exposure in the oral study was less than that in the inhalation study. Toxicokinetic results from previous studies are summarized in Table 3, below.

Table 3: Toxicokinetic Summary for Dogs

Study/ Report #	Dose ($\mu\text{g}/\text{kg}$)	Ciclesonide		Active Metabolite	
		AUC ($\mu\text{g}\cdot\text{h}/\text{L}$)	AUC \div Dose	AUC ($\mu\text{g}\cdot\text{h}/\text{L}$)	AUC \div Dose
DPI 12-month # 116/96	18	1.38	0.077	1.95	0.108
	47	3.20	0.068	4.89	0.104
	92	5.22	0.057	9.84	0.107
DPI 4-week # 205/94	15	---	---	2.06	0.137
	50	---	---	4.89	0.098
	100	---	---	17.18	0.172
DPI 4-week # 184/96	6	0.46	0.077	0.45	0.074
	60	2.53	0.042	3.40	0.057
Oral 4-week # 183/96	40	0.21	0.005	0.24	0.006
	400	1.48	0.004	3.05	0.008
I.V. 2-week # 155/96	20	1.97	0.098	3.11	0.155
	40	1.45	0.036	6.76	0.169
	80	2.99	0.037	15.14	0.189

The data show that plasma concentrations of the active metabolite are proportional to ciclesonide dose. The relative systemic bioavailability by the dry powder inhalation (DPI) route is about 60% while the bioavailability by the oral route is only about 4%.

Based on the previously observed ratio of AUC to dose, the AUC for active metabolite at the high dose in the 12-month oral study would be estimated at only 1 – 2 $\mu\text{g}\cdot\text{hr}/\text{L}$, comparable to the low dose in the 12-month inhalation study. Another approach to compare systemic exposure in the two studies is to compare systemic target organ effects. Effects on adrenal weight are summarized in Table 4, below.

Table 4: Adrenal Effects in 12-month Oral and Inhalation Dog Studies

12-month Inhalation Study			12-month Oral Study		
Dose	Adrenal Weight vs Control		Dose	Adrenal Weight vs Control	
($\mu\text{g}/\text{kg}$)	males	females	($\mu\text{g}/\text{kg}$)	males	females
18	14%↓	35%↓	5	7%↑	2%↓
47	42%↓	41%↓	30	7%↓	10%↓
92	40%↓	62%↓	200	24%↓	41%↓

Based on the extent of decreased adrenal weight, the systemic effect at the high dose in the oral study was intermediate between the low and mid dose in the inhalation study. Thus, both the estimated plasma levels of active metabolite and the extent of adrenal weight decrease suggest that the systemic exposure at the high dose in the oral study was substantially less than in the inhalation study. Therefore, the possibility that the nasal effects seen in the inhalation study were due to systemic exposure has not been entirely ruled out by the lack of nasal effects in the oral study. However, because the severity of the nasal findings are now judged to be of negligible toxicological significance (based on historical control data) it is no longer crucial to determine whether the nasal effects were due to local or systemic exposure.

RECOMMENDATIONS

1. Based on the historical control data submitted by the sponsor, the nasal cavity findings observed in the 12-month dog dry powder inhalation study should be considered a common background finding that may be increased in incidence but not in severity by ciclesonide treatment.
2. Because submitted data have removed the safety concerns for the findings noted above, it is appropriate for the sponsor to use a typical bridging program to relate the toxicity of the HFA ciclesonide formulation to the chronic toxicity profile established for the dry powder. Since 28-day inhalation studies with the HFA formulation have already been submitted, the only additional bridging study needed to support long-term clinical trials is a 90-day study in the most appropriate species. Since both rat and dog exhibit the typical glucocorticoid effects that characterize ciclesonide toxicity, the 90-day dog study proposed by the sponsor is appropriate. This is consistent with the previous determination that a 3-month dog study would be appropriate if the sponsor can provide a satisfactory explanation for the nasal cavity findings in the 12-month dog DPI inhalation study and the histiocytosis in the 6-

month rat inhalation study (see review #3, 05 Nov 97 and minutes of teleconference on 19 Mar 98).

Draft Letter to Sponsor:

b(5)



Mark Vogel, Ph.D., Pharmacologist

Original IND 54,958
c.c. HFD-570/Division File
HFD-570/C.J. Sun
HFD-570/W.M. Vogel
HFD-570/R. Nicklas
HFD-570/L. Cobbs

ATTACHMENT 6.

**HFD-570 DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION**

Review #7

IND number: 53,391

Serial No. N034 YY

Date of submission: 03/19/1999

Reviewer: Huiqing Hao, Ph.D.

Review Completion Date: 06/18/01

Drug: Ciclesonide (Active ingredient B9207-015) MDI

Sponsor: Byk Gulden Pharmaceuticals, Institute of Pathology and Toxicology, Friedrich-Eber-Damm 101, D-22047 Hamburg

Communication to Sponsor: Yes () No (X)

Relevant INDs/NDAs/DMFs: None

Indication: Asthma

Route of administration: Inhalation

Clinical Formulation: White to off-white powder in MDI. Other ingredients: — (w/w) propellant HFA-134a and — (w/w) ethanol.

b(4)

Proposed Clinical Protocol: None

Previous reviews, date and reviewers:

Review #	Submission date	reviewer	completion date
Original review	05/23/1997	Satish Tripathi	08/01/1997
2 (addendum original)	05/23/1997	Satish Tripathi	09/05/1997
3	08/26/1997	Satish Tripathi	11/05/1997
4	12/15/1997	Satish Tripathi	03/20/1998
5 (car. protocols)	05/14/1998	W. M. Vogel	07/08/1998
6	09/08/1998	W. M. Vogel	03/01/1999

Studies reviewed in this submission:

1. Influence on male and female fertility (rat). Effects on early embryo-fetal development. Toxicity of B9207-015 for reproduction after oral administration. (Report No. 153/97)
2. *In vitro* metabolism of [14C] Ciclesonide by animal and human liver microsomes. (Report No. 71/98)
3. Pilot study on the *in vitro* formation of fatty acid esters of the Ciclesonide metabolite B9207-021 by human lung and liver microsomes as compared to budesonide. (Report No. 278/98)
4. Toxicokinetics of ciclesonide in a 6-month oral toxicity in Wistar rats. (Report No. 222/97)
5. Toxicokinetics of ciclesonide and metabolite B9207-021 in a 4-week low-dose inhalation toxicity study in Beagle dogs (aerosol generated from a MDI). (Report No. 156/98)
6. Comparison of the pharmacokinetics of ciclesonide and its metabolites in single dose inhalation studies in Beagle dogs using aerosol generated from dry powder in metered dose inhalers (MDIs). (Report No. 228D/97).
7. Toxicokinetics of ciclesonide and metabolite B9207-021 in a 1-year oral toxicity study in Beagle dogs. (Report No. 238/98)
8. Toxicokinetics of ciclesonide and metabolite B9207-021 in a 1-year inhalation toxicity study in Beagle dogs (aerosol generated from powder). (Report No. 221/97)

Studies have been reviewed previously:

1. Toxicity of B9207/015 in beagle dogs following inhalation from MDI (metered dose inhaler) for 4 weeks. (Report No. 220/97, submitted on 08/26/1997, reviewed by Tripathi on 11/05/1997)
2. The toxicity of B9207-015 after oral administration in the mouse for 3 months (dose range finding, second study). (Report No. 185/95, submitted on 05/23/1997, reviewed by Tripathi on 09/05/1997)
3. The toxicity of B9207-015 after oral administration on the mouse for 3 months (dose range finding, second study). (Report No. 20/97, submitted on 12/15/1997, reviewed by Tripathi on 03/20/1998)
4. Toxicokinetic of Ciclesonide in a 4-week inhalation toxicity study in Sprague-Dawley rats (aerosol generated from powder). (Report No. 197/97, submitted on 12/15/1997, Tripathi 03/20/1998)
5. Toxicokinetic of Ciclesonide in a 6-month inhalation toxicity study in Sprague-Dawley rats (aerosol generated from powder). (Report No. 198/97, submitted on 12/15/1997, reviewed by Tripathi on 03/20/1998)
6. Toxicokinetic of Ciclesonide in a 4-week inhalation toxicity study in Wistar rats (aerosol generated from MDIs). (Report No. 199/97, submitted on 12/15/1997, reviewed by Tripathi on 03/20/1998)

Pharmacokinetics Studies

Metabolism

Study title: *In vitro* metabolism of [14C] Ciclesonide by animal and human liver microsome

Study date: 05/1995-06/1995

Study No. R15/FKM/208

Report No.: 71/98

Conducting Lab: Byk Gulden

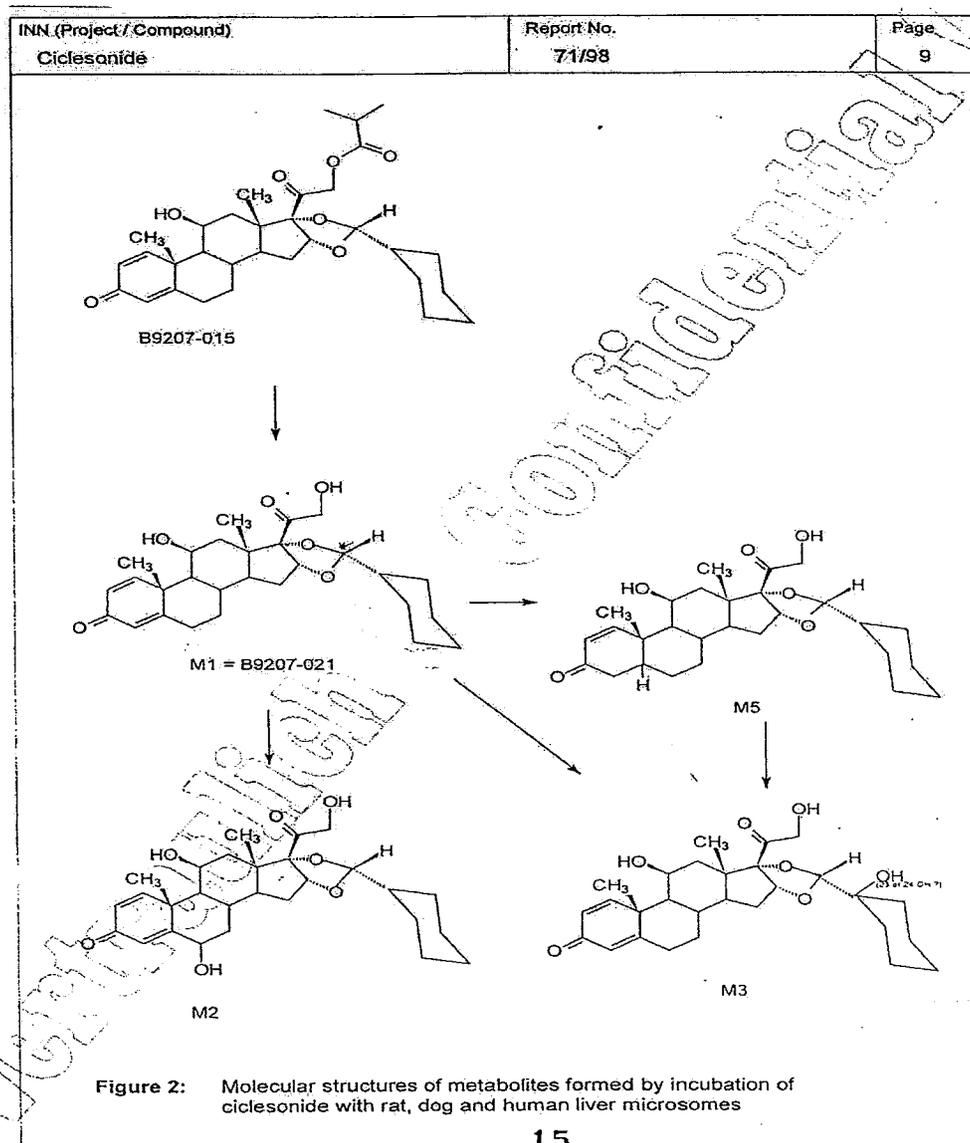
Methods: To examine the interspecies differences in the metabolic profile, [14C]-Ciclesonide (10 µM in methanol) was incubated *in vitro* with microsome protein (0.5mg/kg, from Sprague-Dawley female rats, Beagle dogs or human) in 3 ml assay mixture. Reaction mixture was sampled at designed time points and analyzed for metabolites using TLC. Time 0 was set in the absence of NADPH. (Note: ¹⁴C was labeled at a stable position of the parent compound, therefore, all metabolites carried the radioactivity)

Results: M1 (B9207-021, deesterification product from ciclesonide) was the major metabolite produced by rat and dog microsomes after 1-hour incubation (rat, 52%; dog, 75%). In contrast to dog and rat, human microsome rapidly converted M1 to M2, M3, and M7; these metabolites comprise 79% radioactivity after 1 hour. M2 and M3 represented the 6-hydroxy derivative of M1 and a hydroxy derivative of M1 with -OH group localized in the cyclohexyl moiety of the molecule, respectively. M5 was obtained by reduction of the A-ring of M1 at the 4,5 position. The structure of M7 is unknown. M4 as a metabolite was presented in the results with no further information provided. Further details are shown in the table and figure below.

Metabolite profiles determined by quantitative TLC of the methanolic extracts after incubation of 10 µM [14C]-ciclesonide with rat, dog and human liver microsomes.

Species	Incubation time (min)	% radioactivity extracted with methanol	Radioactive bands (% of spotted material)						
			Ciclesonide	M1	M2	M3	M4	M7	M5
Rat	0	100	59	41	0	0	-	0	0
	15	99	2	83	4	4	-	3	0
	30	99	0	70	10	11	-	8	0
	60	99	0	52	16	16	-	15	0
Dog	0	99	53	47	0	0	-	0	0
	15	99	0	95	2	2	-	0	0
	30	99	0	89	7	4	-	0	0
	60	99	0	75	15	11	-	0	0
Human	0	99	70	30	0	0	-	0	0
	15	99	13	72	7	8	+	-	0
	30	97	0	32	16	14	-	19	13
	60	96	0	8	20	59	+	-	7

+: Presence, -: Absence



Conclusions: *In vitro* metabolism of ciclesonide in the presence of microsomes from rat, dog and human, showed interspecies difference. Common metabolites formed in rat, dog and human microsomes are M1, M2 and M3, while M7 was formed only in rat and human microsomes. M5 was produced only with human microsomes. In human, M1 was rapidly converted to other metabolites.

Study title: Pilot study on the *in vitro* formation of fatty acid esters of the ciclesonide metabolite B9207-021 by human lung and microsome as compared to budesonide.

Study date: 07/27/1998-10/22/1998

Study No.: M15/FKM/202

Report No.: 278/98

Conducting Lab: Byk Gulden

Introduction: Ciclesonide (B9207-015) represents a prodrug that yields the active metabolite B9207-021 by ester cleavage in position 21. Budesonide (B9299-011), a glucocorticoid used for inhalation treatment of asthma, also carries a C21-hydroxyl group. The conjugation of budesonide with fatty acid has been reported. This study was to investigate the *in vitro* formation of palmitate ester of B9207-021 as compared to budesonide.

Methods: Pooled human hepatic and pulmonary microsomes were incubated with [¹⁴C]B9207-021 and Budesonide (B9299-011), in the presence of ATP, CoA and palmitic acid. Formed metabolites and remaining parent compound were detected by HPLC using UV detector. Reversibility of the ester formation was examined by isolating radiolabeled B9207-021 fatty acid esters and incubating them with porcine pancreas lipase to demonstrate the identity of fatty acid ester.

Results: B9207-02 conjugated with palmitic acid *in vitro* in the presence of human liver and lung microsomes. The formation of conjugates was time dependent. Fatty acid ester conjugates were produced with hepatic microsome at levels of 0.2% and 3.3% after reacting for 1 h and 2 hrs, respectively; Fatty acid ester conjugates were produced at levels of 0.6 and 1.2% with lung microsomes after reacting for 1 h and 2 hrs, respectively. The obtained fatty acid esters were lipase substrate. Thus, the reaction of conjugation with fatty acid is completely reversible. Compared with Budesonide, conjugation of B9207-021 with palmitic acid resulted in a similar amount of lipoidal metabolites with higher lipophilicity.

Conclusions: Similar to Budesonide, B9207-021 undergoes *in vitro* reversible esterification.

Pharmacokinetics

Study Titles:

- 1). Toxicokinetics of Ciclesonide in a 6 month oral toxicity study in Wistar Rats (Study No. R15/FKM/101; Study date: 04/1995-07/1998; Report No. 222/97).
- 2). Toxicokinetics of Ciclesonide and metabolite B9207-021 in a 4-week low dose inhalation toxicity study in Beagle dogs [aerosol generated from a MDI (HFA)]. (Study No.H15/FKM/111; Study date: 11/1997-08/1998; Report No. 156/98)
- 3). Toxicokinetics of Ciclesonide and metabolite B9207-021 in a 1-year oral toxicity study in Beagle dogs. (Study No. H15/FKM/109; Study date: 04/1997-10/1998; Report No. 238/98)

4). Toxicokinetics of Ciclesonide and metabolite B9207-021 in a 1-year inhalation toxicity study in Beagle dogs (aerosol generated from powder). (Study No. H12/KFM/106 & 107; Study date: 11/1996-01/1998; Report No. 221/97)

Conducting Lab: Animal studies by _____
_____ Pharmacokinetic
evaluation by Byk Gulden.

b(4)

Methods: Animals were treated with B9207-015 (p.o. in suspension in PEG 400, inhalation in HFA or dry powder as indicated in the titles) and at the designed time points blood samples were collected and analyzed for B9207-015 and/or B9207-021 using HPLC. The lower limit of quantification (LLOQ) was 0.25 ng/ml for B9207-021 using 0.1 ml rat plasma, and 0.025 ng/ml using 1 ml dog serum.

Ciclesonide was rapidly metabolized to pharmacologically active product B9207-021 in vivo. In rat serum samples, only B9207-021 was measured as B9207-015 was converted into B9207-021 by addition of esterase before measuring B9207-021. Thus the measured B9207-021 included also B9207-015.

When dogs were given with ciclesonide via DPI over a one-year period (Report No. 221/97), the day 1 data were generated from different animals than those used to generate 3, 6, and 12-month data.

Results and conclusions: Treatment of dogs with ciclesonide both per oral (0.03-0.2 mg/kg) and inhalation (0.4-12 µg/l aerosol for 30 min) showed similar pharmacokinetic profiles. The animal exposure to ciclesonide as assessed by AUC and C_{max} of both B9207-015 and B9207-021 was approximately proportional to the administered dose. Daily administration up to 1 year showed no dose accumulative effects. Studies of oral treatment at doses of 0.08 to 1.6 mg/kg/day for 6 months in Wistar rat yield no ascertained AUC and T_{1/2} due to the low plasma concentrations and data variability. However, in agreement with the findings in dogs, the C_{max} was proportional to the dose given, and there was no dose accumulative effect over the 6 month repeated treatment. Additionally, the sponsor compared the pharmacokinetics of the two different methods of aerosol generation, MDI and DPI, using the data from previous two different studies with the doses normalized. The sponsor stated that ciclesonide exposure by MDI gave a high C_{max} but the same AUC as those by DPI (Report No. 258D/97). The data from the dog studies (listed in the following table) agreed with this statement regarding to the exposures to both B9207-015 and B9207-021. The following table summaries the pharmacokinetic characteristic of the four studies.

Arithmetic mean values of the pharmacokinetic characteristics of ciclesonide treatments

Animal	Rats (Wistar)				Dogs (Beagle)												
	Oral				Inhalation*				Oral								
Report No.	222/97				156/98				221/97				238/98				
Animal N	6/sex/dose				4/sex/dose				4/sex/dose				5/sex/dose				
Treatment Duration	6 Mon				4 wk				1 year				1 year				
Dose / day	0.08, 0.36, 1.6 mg/kg				1.4, 4, 15 µg/kg/day (0.4, 0.8, 2.5 µg/l for 30min)				18, 47, 92 µg/kg/day (2, 6, 12 µg/l for 30 min)				0.03, 0.2 mg/kg				
	Dose	D1	3mo	6mo	Dose	D1	D24	Dose	D1	3mo	6mo	1 y	Dose	D1	6mo	1 y	
B9207-015					C_{max} (µg/l)				C_{max} (µg/l)				C_{max} (µg/l)				
					1.4	0.319	0.260	18	0.977	0.934	0.987	0.878	0.03	0.088	0.269	0.251	
					4	0.376	0.432	47	2.250	1.982	2.026	1.972	0.2	0.608	1.242	0.889	
					15	2.315	1.608	92	4.344	2.960	2.693	3.166					
					T_{max} (h)				T_{max} (h)				T_{max} (h)				
					1.4			18	0.50				0.03	0.92	0.55	0.67	
					4	0.50		47	0.56	0.50			0.2	0.80	0.90	0.95	
					15			92	0.50								
					AUC				$AUC_{(0-6h)}$ (µg.h/l)				$AUC_{(0-6h)}$ (µg.h/l)				
					1.4	n.a.		18	1.33	1.42	1.61	1.35	0.03	n.a.			
					4			47	3.25	3.14	3.36	3.34	0.2	0.77	1.34	1.03	
					15			92	6.22	4.64	4.90	5.37					
				$T_{1/2}$ (h)				$T_{1/2}$ (h)				$T_{1/2}$ (h)					
				1.4			18				0.03	n.a.					
				4	n.a.		47	n.a.			0.2	0.69	1.19	0.57			
				15			92										
B9207-021					C_{max} (µg/l)				C_{max} (µg/l)				C_{max} (µg/l)				
	0.08	n.a.			1.4	0.151	0.123	18	0.655	0.463	0.554	0.501	0.03	0.101	0.231	0.134	
	0.36**	0.351	<0.25	0.310	4	0.233	0.220	47	1.498	1.126	1.449	1.320	0.2	1.049	1.679	1.170	
	1.6	1.378	1.188	0.986	15	1.446	0.974	92	3.026	1.322	1.883	2.290					
					T_{max} (h)				T_{max} (h)				T_{max} (h)				
	0.08	n.a.			1.4	0.81	1.00	18	1.00	1.00	1.19	1.13	0.03	1.40	0.95	1.00	
	0.36**	0.5	1.00	0.25	4	0.88	0.75	47	0.94	1.00	1.13	1.21	0.2	1.15	1.25	1.60	
	1.6	0.52	1.06	1.03	15	0.56	0.75	92	0.81	1.31	1.19	1.31					
					AUC				AUC^1				AUC^2				
	0.08				1.4	0.28	n.a.	18	2.10	1.74	2.20	2.02	0.03	n.a.	0.68	0.53	
	0.36	n.a.			4	0.49	0.52	47	5.11	4.40	5.37	5.52	0.2	3.04	4.45	3.20	
	1.6				15	2.83	2.25	92	17.74	5.76	7.73	9.13					
				$T_{1/2}$ (h)				$T_{1/2}$ (h)				$T_{1/2}$ (h)					
0.08				1.4			18				0.03	2.5	2.3	1.77			
0.36	n.a.			4	1-2 hr		47	n.a.			0.2	1.6	1.8	1.8			
1.6				15			92										

n.a. Not ascertained; * doses indicated were target aerosol concentration; ** median value; ¹, $AUC_{(0-\infty)}$ (µg.h/l); ², $AUC_{(0,24)}$ (µg.h/l). **B9207-021** in rat serum included B9207-015 (see methodology section).

Reproductive Toxicology

Study Title: Influence on male and female fertility (rat):

Study Date: 01/1997-02/1998

Study No. RR0468

Report No. 153/97

Conducting Lab: Byk Gulden

GLP: The report was accompanied with a signed GLP statement.

QA report: Yes.

Methods:

Wistar rats (28/sex/group) were orally given B9207-015 (in PEG 400 suspension) daily at 0, 0.1, 0.3 or 0.9 mg/kg (The no-effect dose for maternal was 0.1mg/kg and for embryo-fetal development 0.9mg/kg). Previous histopathology examination (Study 223/95, 08/20/1996, Vol. C2.12, see review by Dr. Tripathi 03/20/1998) demonstrated that dose up to 1.6 mg/kg for 6 months caused no toxicity to male reproductive organs. Therefore in the current study, males were dosed 4 weeks prior to mating and continued during mating time (up to 3 weeks) until autopsy of respective female has proven pregnancy. For females, treatment started 14 days prior to mating and continued during mating time (up to 3 week) until day 14 post-coitus.

Males which did not copulate or whose corresponding female failed to pregnant despite of evidence of spermatozoa were again mated with untreated females until spermatozoa appear in vaginal smear or up to 3 weeks at the most. In both male and female dosed groups, treatment continued until autopsy.

Parameters and endpoints evaluated:

- Behavior and appearance: Daily.
- Mortality
- Body weight: Day 1 and twice a week thereafter. Females were weighted daily during pregnancy.
- Food consumption: Twice a week except during mating time. From female pregnancy, females daily and males weekly.
- Pre-coital interval.
- Copulation index.
- Autopsy and spermatology: In the case of disturbed fertility, histology of testes and epididymis were examined. Spermatology was examined in all males for motility and count of sperm.
- Vaginal smear and estrus cycle: Morning after overnight mating.

- Autopsy of dams: Fertility rate, implantation rate, preimplantation loss, and postimplantation loss.

Results:

Behavior and general appearance: Normal

Mortality: 4 rats died in cage, 1 male control (day 20), 1 male (day 25) and 2 females (day 7 and 25) in 0.9mg/kg group, those deaths were not considered drug-related. Similar findings were reported in previous 6 month study (rats 26-wk oral toxicity, Vol C2.12, submitted on May 23, 1997, reviewed by Dr. Tripathi dated 06/03/1997) in which the similar mortality rates were found in both control and treated animals.

Body weight: Compared to the corresponding controls, males of the 0.9mg/kg group showed a 43% decrease in body weight gain at end of treatment (day 44). Females of the 0.9mg/kg group showed decreased body weight gain during the whole treatment period including the time of pregnancy (29% decrease at day 30). Details of the body weight gains are presented in the table below.

Dose (mg/kg)	0		0.1		0.3		0.9	
Sex	M	F	M	F	M	F	M	F
Day	Mean Body Weight Gain (g)							
1	0	0	0	0	0	0	0	0
9	12	7	13	5	11	5	4	-1
16	19	8	21	6	17	8	7	0
22*		23		26		23		14
30*	30	45	31	45	27	43	16	32
44	47		45		41		27	

* Females in these days included only those pregnant at day 14 post-coitus (female numbers: 0 dose, 21; 0.1mg/kg, 28; 0.3mg/kg, 26; 0.9mg/kg, 24).

Food consumption: Food consumption in males was significantly reduced in all drug-treated groups during week 3 and groups of 0.1 and 0.9 mg/kg during week 2. For females of the 0.9 mg/kg group, food consumption was significantly reduced during the whole treatment period. The details are presented in the table below:

Dose (mg/kg)		Mean animal food consumption (mg/kg)			
Week		0	0.1	0.3	0.9
Male	1	21.7	21.1	21.1	20.9
	2	22.2	21.2*	21.3	20.6*
	3	22.4	21.6*	21.4*	21.2*
	4	23.3	22.4	22.4	22.5
Female	1	16.1	15.7	15.5	14.6*
	2	16.5	16.1	16.2	15.2*
	3	18.0	18.1	17.7	16.9*
	4	19.3	19.3	19.4	18.4*

*Significant different from the 0 dose group.

Reproductive toxicology: No substance related findings except that one female of 0.3 mg/kg group showed total fetal resorptions. The following table summarizes the reproductive toxicology data.

Dose (mg/kg)		0	0.1	0.3	0.9	
Parents	Pre-coital intervals	No substance related findings				
	Copulation index	No substance related findings				
	Testes weight	No substance related findings				
	Females observed	28	28	28	28	
	Females with sperm	28	28	28	28	
	Pregnant females	21	28	26	22	
	Females with resorptions only			1		
Litters	Arith. Mean per litter	Corpora lutea	13	12.5	12.6	13.1
		Implantations	12	11.4	11.3	11.8
		Live fetuses	11.7	10.9	10.8	11.4
		Preimpl. Loss	7.1	9.6	11.4	10.1
		Postimpl. Loss	2.8	3.6	8.6	3.0
		Sperm motility %	76	75	73	72
		Sperm count (mil. /g cauda epididymis)	144	408	460	445

Conclusion:

Oral treatment of Wistar rats with ciclesonide (0.1 to 0.9 mg/kg/day) showed no toxicity for fertility, in spite of the effects of reducing body weight gains in both parental animals and reducing food consumption. Therefore, the NOAEL for reproductive toxicity segment I is 0.9 mg/kg in Wistar rats.

Overall Summary and Evaluation

Pharmacokinetics: Ciclesonide was rapidly absorbed upon administration per oral and inhalation in rats and dogs. The C_{max}s were reached at 0.6-1 hr after oral administration and 0 time after inhalation. Following absorption, ciclesonide was metabolized into several different products and the major one M1 (B9207-021) was pharmacologic active. C_{max} of B9207-021 was reached about 0.5 hour after that of ciclesonide. *In vitro*, human microsome rapidly converts M1 into other metabolites. The *in vitro* study found that metabolic reaction from ciclesonide to M1 was reversible. The AUC was approximately proportional to the dose administered. Daily treatment, up to 6 months and 1 year in rats and dogs respectively, did not show any dose accumulative effect. The studies in dog showed that the drug exposure (AUC) via MDI (HFA) formulation was comparable to that via DPI formulation. Similarly, previous submission (12/15/1997) showed that the drug exposure in dogs with a single inhalation was dose-dependent, while MDI and DPI formulation gave the comparable exposure.

Reproductive toxicity: Reproductive toxicology studies of segment II for ciclesonide have been performed in SD rats and rabbits (original submission). The drug was neither embryo/fetotoxic nor teratogenic in SD rats at dose up to 0.9 mg/kg/day. However, this drug was fetal toxic and teratogenic in rabbits at 25 µg/kg/day and above. In the current submission, this drug (up to 0.9 mg/kg/day) showed no adverse effect on fertility in SD rats.

Recommendations: None at this time.

Huiqing Hao, Ph.D., Pharmacologist

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Huiqing Hao
6/20/01 01:13:10 PM
PHARMACOLOGIST

Joseph Sun
6/20/01 01:18:09 PM
PHARMACOLOGIST
I concur.

ATTACHMENT 7.

**HFD-570 DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION**

Review 8

IND number: 53,391

Serial No. N057YY, N063 SM, N071 PN, PI, N-113PN.

Date of submission: 03/13/00, 08/17/00, 12/21/00, 08/03/01.

Reviewer: Huiqing Hao, Ph.D.

Review Completion Date: 12/12/01

Communication to Sponsor: Yes (X) No ()

Sponsor: Byk Gulden Lomberg Chemische Fabrik GmbH, Germany

Drug: Ciclesonide (Active ingredient B9207-015)

Relevant INDs/NDAs/DMFs: None.

Drug class: Glucocorticoid Steroid

Indication: Asthma

Route of administration: Oral Inhalation (MDI)

b(4)

Clinical Formulation: MDI with HFA-134a propellant and — ethanol

Proposed clinical dose and duration: Phase III, up to 800 µg/day for 12 weeks and one year in adults, and up to 200 µg/day for 12 weeks and one year in children.

Previous reviews, date and reviewers:

Review No.	Submitted	Reviewer	Reviewed
1	02 Jun 97	S. C. Tripathi	01 Aug 97
2	02 Jun 97	S. C. Tripathi	05 Sep 97
3	02 Jun 97, 26 Aug 97	S. C. Tripathi	05 Nov 97
4	15 Dec 97	S. C. Tripathi	20 Mar 98
5	14 May 98	W.M Vogel	08 Jul 98
6	08 Sep 98	W. M Vogel	01 Mar 99
7	19 Mar 99	Huiqing Hao	18 Jun 01

Studies reviewed in the submission dated Mar. 13, 2000

No.	Submission	Study No.	Report No.	Vol./Page
1	Inhibition of CD-3 mediated proliferation of human PBMC by ciclesonide metabolite and its steroid analogs.	BY9010	7/99	3/15
2	Binding affinities of ciclesonide metabolites with glucocorticoid receptors	R15/FKM/106	266/99	5/1
3	Whole body autoradiography in rats after an i.v. or oral dose	R15/FKM/216	214/99	5/55
4	Placental transfer and mammary glandular passage in rats	R15/FKM/214	172/99	10/1
5	<i>In vitro</i> metabolism (dog liver slices and microsomes)	H15/FKM/205	280/99	3/182
6	Metabolism of ¹⁴ C-Ciclesonide in rats	R15/FKM/212	252/99	3/162
7	PK: single oral and i.v. in mouse.	N15/FKM/202	194/99	3/52
8	TK in Carcinogenesis with MDI in rats	R15/FKM/105	177/99	3/203
9	TK in 3-mon dog study	R15/FKM/112	19/99	4/1
10	Toxicity study in dogs for 3 mon by MDI and DPI	HD0555	273/98	6/1
11	Reverse mutation test in bacteria	S065M0B900	44E/99	5/347
12	Immunostimulation in guinea pigs (ASA and PCA)	SO65HOG300	48E/99	10/73
13	Antigenicity study in mice-rats (PCA)	SO65HOM300	49E/99	10/95

PHARMACOLOGY

Inhibition of CD-3 mediated proliferation of human peripheral blood mononuclear cells by BYK20432, BYK20702, BYK54297, BYK55327 and BYK54609

Background: R-Ciclesonide was developed _____ than S-Ciclesonide _____ (see original review). BYK20432 is a metabolite of R-Ciclesonide.

Results: The following table shows the results from 4 independent experiments.

b(4)

Inhibition of CD3-stimulated PBMC by test compounds (IC50 [nM])

	M1 BYK20432	Budesonide BYK20702	Fluticasone- propionate BYK24297	Rofleponide BYK55327	Mometasone -furoate BYK54609
Expt. No.					
ST 681	2.37	2.60	0.31	0.69	0.27
ST 685	0.85	0.87	0.10	0.17	0.09
ST 686	3.33	2.81	0.31	0.60	0.38
ST 696	3.01	2.64	0.37	0.40	0.25

Conclusion: The metabolite (M1) of the R-epimer of Ciclesonide inhibited the CD3-induced proliferation of human PBMC. In this system, M1 was as potent as Budesonide, but less potent than Fluticasonepropionate, Rofleponide and Mometasonefuroate.

Binding affinities of ciclesonide metabolites M2, M3a and M5 in the glucocorticoid receptor binding assay

Method:

Hepatic fractions were prepared from SD rats (1000g supernatant) and from guinea pigs (microsomes). Fractions were incubated with B9207-021 in the presence of NADPH. Metabolites were purified using HPLC. The isolated metabolites were tested in a glucocorticoid binding assay. The compounds were tested for binding affinity with glucocorticoid receptors. Additionally, budesonide and B9207-021 were tested and dexamethasone was used as reference.

Results:

The three major metabolites M2 (hydroxylated in position 6), M3a (hydroxylated in position 24) and M5 (reduced in the A-ring at position 4 and 5) were isolated from in vitro incubation using B9207-021 as substrate. The binding properties to glucocorticoid receptor (IC50) were evaluated and normalized to dexamethasone. Relative IC50 valued of 8.9, 7.6 and 1.9 and 0.5 were calculated for metabolites M5, M2, M3a, and M1 respectively. The binding affinity of M1 was about the same as that of Budesonide.

Conclusions: The binding affinity with glucocorticoid receptors were lower in M2, M3a and M5 than M1(B9207-021). B9207-021 was similar to Budesonide, but higher in comparison with dexamethasone, regarding to binding affinity to the glucocorticoid receptor.

SAFETY PHARMACOLOGY

Intraperitoneal administration at dose up to 10 mg/kg , B9207-015 and B9207-016 has no influence on urine parameters (volume, pH, osmolality, electrolytes) and serum parameters (glucose, electrolytes) as compared to control.

PHARMACOKINETICS AND TOXICOKINETICS

One pharmacokinetics study in mice and two toxicokinetics studies, one in rats and one in dogs were performed.

Note: For the study in mice and rats, due to the high esterase activity in mouse serum, a reliable simultaneous measurement of ciclesonide and B9207-021 is not possible. Therefore, in the serum samples, only B9207-021 was measured while ciclesonide was converted into B9207-021 by addition of esterase before measurement.

In the pharmacokinetics study (Study No. N15/FKM/202, Report No. 194/99), male mice (5/dose/timepoints) were given a single dose of [¹⁴C]-ciclesonide orally or intravenously. Blood samples were collected at designed timepoints and Serum concentrations of total radioactivity, ciclesonide and metabolite B9207-021 were measured by using HPLC and liquid scintillation counting. LLOD and LLOQ were 0.05 and 0.25 ng/ml, respectively, for sample volume of 0.1 ml.

Following an intravenous dose of [¹⁴C]ciclesonide, total radioactivity declined in a $T_{1/2}$ of 3.9 hr, whereas, sum of ciclesonide and B9207-021 declined in a $T_{1/2}$ of 1.8 hr. Thus, the bulk of the total radioactivity was composed of compounds other than ciclesonide and B9207-021 (fig. 2 in the next page).

Following an oral administration, about 30% radiolabeled material was absorbed. However, concentration of total radioactivity at C_{max} were about 50 to 80 times higher as compared to the sum of ciclesonide and B9207-021 (fig. 3 in the next page), suggesting significant first-pass effect and rapid conversion of B9207-021 into other metabolites. The bioavailability is far below 30% calculated for absorption.

The following two tables show geometric mean PK parameters of total radioactivity and serum B9207-021 following a single oral or intravenous dose ¹⁴C-ciclesonide.

Total radioactivity

	C _{max} (ng equiv./ml)	T _{max} (h)	AUC _(0-8h) (ng equiv.h/ml)	T _{1/2} (h)	V _{d,area} (l/kg)	Cl (l/h/kg)
i.v. (0.9mg/kg)	-	-	525.79	3.93	9.71	1.71
p.o. (0.45 mg/kg)	30.8	0.35	73.64	3.24	-	-
p.o. (0.9 mg/kg)	60	0.30	167.40	3.50	-	-
p.o. (1.35 mg/kg)	66.4	0.60	185.60	3.85	-	-

Serum concentration of B9207-021

	C _{max} (ng equiv./ml)	T _{max} (h)	AUC _(0-8h) (ng equiv.h/ml)	T _{1/2} (h)	V _{d,area} (l/kg)	Cl (l/h/kg)
i.v. (0.9mg/kg)	-	-	177.28	1.78	13.01	5.08
p.o. (0.45 mg/kg)	Not obtained due to plasma B9207-021 rapidly declined to undetectable level.					
p.o. (0.9 mg/kg)						
p.o. (1.35 mg/kg)						

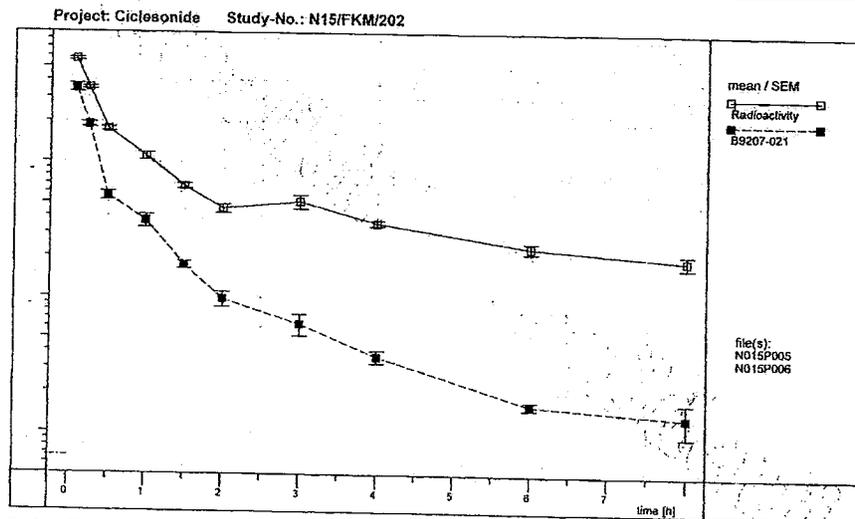


Fig. 2: Time course of concentrations of total radioactivity and B9207-021 in mouse serum following a single intravenous dose of 0.9 mg/kg [¹⁴C]-ciclesonide (n=5/timepoint)

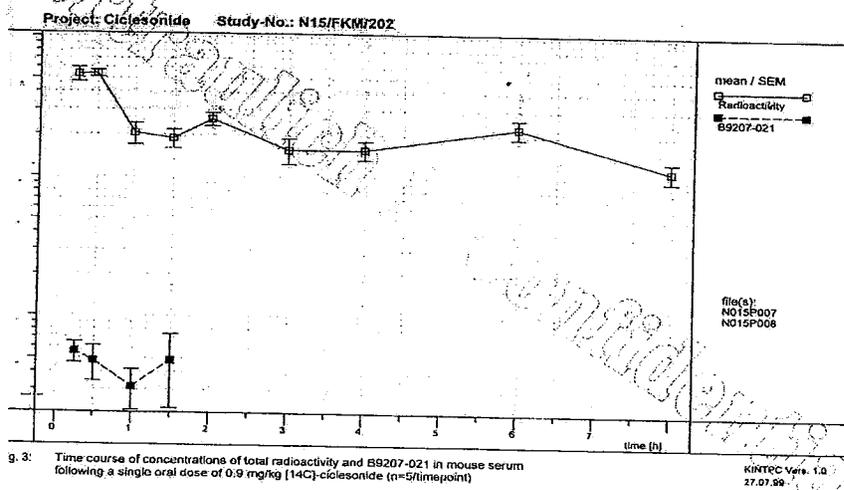


Fig.3

The toxicokinetics study in rats (Study No. R15/FKM/105, Report No. 177/99) was performed as a part of procedure for an inhalative carcinogenicity study. Wistar rats (6/sex/timepoint) were exposed to ciclesonide by aerosol generated from MDI for 1 hour per day, consecutive 724 day. At day 366 and day 724, blood samples were collected at designed timepoints (1, 2, 6, and 22h after the exposure) and concentrations of B9207-021 were analyzed by HPLC. Lower limit of quantification was 0.25 µg/l using 50 µl serum.

In the HD (6.25µg/L) and MD (2.5 µg/L) group, maximum serum concentration was observed at the first available timepoint (1h after the end of inhalation) which were in proportion to the dose level and were remained constant through out the study. T_{1/2} was not obtained due to limited number of timepoints. AUC_(0-6h) were estimated for the HD based on data from 1h to 6h post-dose. No sex associated differences were seen in the pharmacokinetic parameters.

Serum concentrations of B9207-021 at 1h following inhalation and AUC_(0-6h) of the HD.

	Day 1			Day 366			Day 724		
Aerosol conc. (µg/l)	1	2.5	6.25	1	2.5	6.25	1	2.5	6.25
Serum conc. of B9207-021 (µg/l)	NA	0.525	1.490	0.424	0.837	2.247	0.250	0.528	1.693
AUC _(0-6h after inhalation) (µg.h/l)			3.03			6.70			4.95

The toxicokinetics study (Study No. R15/FKM/112, Report No. 19/99) in dogs was a part of 3-month inhalation toxicity study. In this study, Beagle dogs (4/sex/group) were exposed to ciclesonide aerosol generated from MDI or DPI, 30 min daily for 87 days. At day one and day 87, blood samples were collected (pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6 and 24 hr post-dose) and analyzed for the parent compound (B9207-015) and active metabolite

(B9207-021) by HPLC. The LLOQ was 25 pg/ml for ciclesonide and its metabolite using 1 ml dog serum.

The drug exposures (C_{max} and AUC) were proportional to the dose administered and were constant throughout the study. AUC was not influenced by the method of aerosol generation. However, C_{max} was higher following inhalation of aerosol generated from a MDI.

PK parameters of B9207-015 following inhalation of ciclesonide (MDI or DPI) in dogs

Group	Dose in inhaled air (µg/l)	Day 1		Day 87	
		C _{max} (µg/l)	T _{max} (h)	C _{max} (µg/l)	T _{max} (h)
2 (MDI)	2	1.321	0.5	1.279	0.5
3 (MDI)	7	4.490		3.930	
4 (MDI)	15	9.174		8.742	
5 (powder)	15	5.706		4.252	

PK parameters of B9207-021 following inhalation of ciclesonide (MDI or DPI) in dogs.

Group	Dose*	Day 1				Day 87			
		C _{max}	AUC _(0,inf)	T _{max}	T _{1/2} **	C _{max}	AUC _(0, 24)	T _{max}	T _{1/2} **
2 (MDI)	2	0.760	1.56	0.81	2.29	0.733	2.09	1.00	2.80
3 (MDI)	7	2.449	4.91	0.75	1.72	1.986	5.18	0.94	1.70
4 (MDI)	15	6.089	15.49	0.94	4.02	5.177	15.92	1.00	5.96
5 (powder)	15	3.570	16.54	1.38	4.04	3.212	16.36	1.13	5.59

Unit for PK parameters: C_{max}, µg/l; AUC, µg.h/l; T_{max}, h. * target concentration of B9207-015 in inhaled air (µg/l), **, estimated up to 24 h for group 4 and 5.

DISTRIBUTION

Whole –body autoradiographic study of [¹⁴C]-ciclesonide in the rat following a single intravenous and oral dose

Method: Male Wistar rats (16 total) were given a single dosed of [¹⁴C]-ciclesonide 1mg/kg intravenously (9 animals, each at 2.5 ml/kg) or orally (7 animals, each at 10 ml/kg). Visual estimation of qualitative distribution of radioactivity were performed at 2min (i.v. only), 5min (i.v. only), 15min, 30min, 1h, 4h, 8h, 24h, 48h post dosing.

Results:

At 2 min after dosing, radioactivity concentration was highest in lungs and myocard, moderate in kidneys and liver, low in the brain.

At 5 min, highest radioactivity was seen in liver and myocard followed by kidneys. Low concentrations were seen in lungs and stomach wall.

At 15 and 30 min, high concentration of radioactivity was seen in intestinal contents, followed by liver and salivary glands. Brain contained very low levels of radioactivity.

With time, radioactivity was excreted and appeared in appreciable concentrations in large intestine and faces

At 24 and 48h, a further decrease of radioactivity was seen with discernible amount in large intestine, liver and fat.

Oral dose was moderately absorbed as highest concentration were seen in stomach and intestine with lower amounts being found in the liver and much in other organs. 4h after dosing, radioactivity was located in feces and large intestine, with lower amounts occurring in liver. At 8h, radioactivity was excreted via feces. With time, concentrations of radioactivity decreased with low levels being found in large intestine, fat and liver at 24 and 48h.

Placental transfer and mammoglandular passage of [¹⁴C]-ciclesonide in the rat

Methods: Study design is presented in the following table. At designed timepoints, sample radioactivity was measured.

Study	Route	Dose (mg/kg)	Animal (Wistar rats)	Sampling time (hrs post-dose)	samples	Animal # per time points
Placental transfer	i.v.	0.16	14 th day of gestation	1, 4, 8, 24	Blood, selected tissues*	3
			18 th day of gestation			
	p.o.	0.9	14 th day of gestation			
			18 th day of gestation			
Whole body autoradiography	i.v.	0.16	18 th day of gestation	1, 4, 8, 24		1
	p.o.	0.9				
Mammary excretion	i.v.	0.16	4 day after parturition	1, 4, 8, 24 h for milk; 24 h for tissues	Milk from pups and tissues of dams and pups**	5 for each route of dosing
	p.o.	0.9				

Selected tissues: brain, heart, lungs, liver, spleen, eyes, mammary glands, adrenals, thymus, kidneys, adrenals, placenta, fetuses and amniotic fluid. Dam tissues collected were the same as for pregnant rats except placenta, fetuses, and amniotic fluid. Pups' liver was also collected for radioactivity.

Results:

Placental transfer:

After an i.v. dose of [¹⁴C]-ciclesonide to rats in the 14th day of gestation, highest radioactivity was observed in maternal liver, lungs, adrenals, and kidneys. Maternal plasma levels were lower than in these tissues. Very small amount of drug passed placenta as evidenced by low radioactivities in fetus and amniotic fluid (see the table below). A similar distribution profile was observed when the rats were on day 18th of gestation.

Pharmacokinetic profile on Day 14 of gestation.

Organ/tissue	C _{max} (µg equiv./g)	T _{max} (h)	AUC _(0-24h) (µg equiv.h/g)	$\frac{C_{max, tissue}}{C_{max, plasma}}$	$\frac{AUC_{tissue}}{AUC_{plasma}}$
Plasma	0.035	1	0.17	-	-
Liver	0.512	1	3.21	14.6	18.9
Lungs	0.338	4	3.21	9.7	18.9
Adrenals	0.130	1	0.87	3.2	5.1
Kidneys	0.129	1	0.91	3.7	5.4
Mam. Gland	0.116	1	1.01	3.3	5.9
Fetus	0.010	1	0.07	0.3	0.4
Amini. Fluid	0.002	1	0.04	0.06	0.2
Placenta	0.058	1	0.35	1.7	2.0

After an oral dose of [¹⁴C]-ciclesonide to rats in the 14th day of gestation, highest concentrations of radioactivity were observed in liver followed by kidneys and adrenals. Maternal plasma, lungs, and heart contained moderate levels of radioactivity. Very limited placental transfer was observed. On Day 18 of gestation, higher total radioactivity than 14th day of gestation, and higher placenta transfer were observed (tissue/plasma AUC ratio was 0.2 for amniotic fluid and 0.4 for fetus).

Pharmacokinetic data after oral dose on Day 14 of gestation.

Organ/tissue	C _{max} (µg equiv./g)	T _{max} (h)	AUC _(0-24h) (µg equiv.h/g)	$\frac{C_{max, tissue}}{C_{max, plasma}}$	$\frac{AUC_{tissue}}{AUC_{plasma}}$
Plasma	0.016	1	0.13	-	-
Liver	0.219	1	3.08	13.7	23.7
Lungs	0.015	1	0.21	0.9	1.6
Adrenals	0.023	1	0.27	1.4	2.1
Kidneys	0.046	1	0.50	2.9	3.8
Mam. Gland	0.009	4	0.14	0.6	1.1
Fetus	n.d	-	0.00	-	-
Amini. Fluid	0.001	1	0.02	0.06	0.2
Placenta	0.014	8	0.19	0.9	1.5

Whole-body autoradiography:

Following an i.v. dose of 0.16 mg/kg [¹⁴C]-ciclesonide to pregnant rats, the highest radioactivity concentrations were identified in maternal gastrointestinal contents, liver, salivary and Harder's glands, and placenta. Very low levels of radioactivity were seen in fetus and amniotic fluid at 1h post-dose. In another word, very limited drug passed placenta. With time, radioactivity was located in feces, large intestine and to a lower level in the liver. Following an oral administration, a similar feature of distribution pattern was observed.

Milk secretion of [¹⁴C]-ciclesonide:

A significant amount of [¹⁴C]-ciclesonide and/or its metabolites were detected in milk after an i.v. (0.16mg/kg) dose to lactating rats. The radioactivity in the milk reached 0.075 µg. equiv./g at 1h after dosing. By 24h, radioactivity in milk was still higher than

that of most maternal tissues and was 25-fold of plasma level. The similar profile of milk secretion was observed after an oral dose of 0.9 mg/kg. The following table shows the time course of radioactivity found in milk and pups' liver after an i.v. dose of [¹⁴C]-ciclesonide.

Time post-dose (h)	Milk (µg equiv./g)	Liver (µg equiv./g)
1	0.075	0.006
4	0.041	0.001
8	0.010	<0.001
24	0.025	0.004

Tissue distribution of radioactivity in lactating rats after an i.v. or oral dose of [¹⁴C]-ciclesonide showed a similar pattern to that in pregnant rats. The following table presents the tissue distributions after an i.v. dose to lactating rats.

Tissue radioactivity (µg equiv./g tissue) in dams 24h after an i.v dose of 0.16 mg/kg [¹⁴C]-ciclesonide

Thymus	Lungs	Heart	Liver	Spleen	Adrenals	Kidneys
0.006	0.003	0.002	0.011	0.003	0.008	0.008
Eye	Brain	Mammary gland	Blood	Plasma		
<0.001	<0.001	0.008	0.009	0.001		

METABOLISM

In vitro metabolism of ciclesonide in the dog using precision-cut liver slices and liver microsomes

b(4)

Method: [¹⁴C]-B9207-015 was incubated with liver slices from Beagle dogs for 6 hrs or with hepatic fractions (cytosol and microsome) from the same dogs for 3 hrs. The metabolites and remaining parent compound were analyzed by HPLC using _____

Results:

There are pronounced differences in metabolite profile using different in vitro metabolism system. Conjugates were only obtained when liver slices were used. Unchanged parent compound was observed using cytosolic fraction but not microsomal fraction or liver slices, suggesting less profound metabolism in cytosolic fraction culture system. The details of metabolite profiles are presented in the table below.

	B9207-015	B9207-021	M2	M3 family	M5	M1 glucuronide	M5 glucuronide
	% of total radioactivity in the chromatogram						
Liver slices	n.d.	5.1	3.7	3.0	n.d.	65.3	13.3
Microsomal fraction	n.d.	33.1	29.9	21.2	n.d.	n.d.	n.d.
Cytosolic fraction	22.2	58.9	n.d.	n.d.	17.3	n.d.	n.d.

Furthermore, B9407-044 is structure related compound and represents only position 21 as possible site of conjugation to hydroxy group. By analyzing the products from incubation of B9407-044 with liver slices, it is concluded that ciclesonide conjugated at position 21 of the molecules following cleavage by esterase(s). This does not, however, preclude that ciclesonide might also be conjugated at position 11 of the molecule and other positions following hydroxylation.

The metabolism of [¹⁴C]-ciclesonide in the rat

b(4)

Method: Total radioactivity in plasma and tissue were measured by LSC. Unchanged drug and metabolites were separated and quantified by μ -TLC.

Dosing

Species/strain:	SD male rats
N:	5/time point
Dose:	1 mg/kg for each route of administration
Frequency:	Single dose
Route:	Oral, i.v., or intratracheally (i.t)
Volume:	p.o., 10 ml/kg; i.v., 2.5 ml/kg; i.t., 0.11 ml/kg.
Formula:	Solution with PEG for oral, with propylene glycol and ethanol for i.v and i.t routes.

Observations and times: Plasma and selected tissues (liver, lungs and kidneys) were analyzed at the following post-dose time points:

i.v.: 2 min, 5 min, 10 min, 20 min, 40 min, 1 h, and 2 h.

p.o.: 15 min, 30 min, 1 h, and 4 h.

i.t.: 2 min, 5 min, 15 min, 30 min, 1 h, and 2 h.

Results:

Stability of [¹⁴C]-ciclesonide in rat plasma:

Rat plasma spiked with [¹⁴C]-ciclesonide at a concentration of 1 μ g/ml showed that ciclesonide decreased to 51% during the first hour incubation, while metabolite M1 amounted to 49%, suggesting the presence of esterase activity in rat plasma.

Ciclesonide metabolite profiles in rat plasma:

After an i.v. dose, M1 represented about 30% of total radioactivity in plasma within 2h, while ciclesonide decreased from 32% at 2min to 7% at 2h. Many other metabolites increased with time. A similar profile was observed after an i.t. dose. After an oral dosing, ciclesonide and M1 represented only small portion of total radioactivity at 15 min post-dose and even smaller in later time-point, suggesting there is a pronounced first-pass metabolism.

Tissue metabolite pattern differed from plasma metabolite pattern in as much as metabolite M1 was the major carrier of radioactivity in lungs, liver and kidneys

regardless of route of administration. Unchanged ciclesonide was only present in small amounts suggesting that appreciable amounts of esterase present in these tissues.

Details of metabolite profile in rat plasma and tissues are shown in the four tables below.

Metabolic profiles in rat plasma

Route of administration	Time post-dosing (min)	% radioactivity extracted with MeOH	Radioactive bands (% of spotted material)								
			Ciclesonide	M1	M2	M3	M4	M6	M13	M14	Origin
i.v.	2	99	32	30	-	4	4	-	4	2	2
	120	92	7	28	-	6	4	-	10	6	31
p.o.	15	96	3	5	2	15	-	3	25	22	12
	240	89	0	2	3	17	-	4	22	18	18
i.t.	2	99	33	36	-	-	-	-	11	8	6
	120	94	6	38	2	8	-	4	5	8	22

Note: only the data of the start and end time points are cited from the report.

Metabolic profiles in rat lungs

Route of administration	Time post-dosing (min)	% radioactivity extracted with MeOH	Radioactive bands (% of spotted material)								
			Ciclesonide	M1	M2	M3	M4	M6	M13	M14	Origin
i.v.	2	99	1	89	0	1	5	0	0	0	0
	120	96	9	53	0	3	14	0	3	0	6
p.o.	15	96	35	46	1	2	0	0	3	2	2
	240	79	6	29	4	9	2	4	5	6	10
i.t.	2	99	11	67	1	1	3	0	0	2	0
	120	97	16	60	3	1	12	0	0	0	2

Metabolic profiles in rat liver

Route of dosing	Time post-dosing (min)	% radioactivity extracted with MeOH	Radioactive bands (% of spotted material)													
			Ciclesonide	M1	M2	M3	M5	M6	M7	M8	M9	M10	M11	M12	M14	Origin
i.v.	2	99	-	50	8	20	7	0	0	2	2	0	0	0	1	2
	120	79	-	3	4	9	1	5	3	5	12	13	11	6	4	13
p.o.	15	87	-	5	5	15	1	5	5	6	14	3	5	8	5	7
	240	72	-	2	11	9	-	4	-	5	11	8	10	9	3	11
i.t.	2	96	12	64	5	4	-	-	-	-	-	-	-	-	8	2
	120	75	-	5	6	9	-	9	4	4	11	7	9	6	5	16

Metabolic profiles in rat kidneys

Route of administration	Time post-dosing (min)	% radioactivity extracted with MeOH	Radioactive bands (% of spotted material)								
			Ciclesonide	M1	M2	M3	M4	M5	M13	M14	Origin
i.v.	2	100	1	88	-	-	2	3	-	-	-
	120	98	3	44	3	3	35	3	-	3	9
p.o.	15	97	18	23	2	7	-	-	14	19	4
	240	89	1	11	4	10	-	2	7	9	16
i.t.	2	99	-	36	-	-	-	-	-	64	-
	120	97	-	36	5	4	27	-	-	3	17

PK/TK CONCLUSIONS:

[¹⁴C]-ciclesonide given to male rats by i.v. was rapidly distributed to lungs and myocard, followed by intestinal content, liver, and salivary glands. Oral dose was moderately absorbed and low concentrations were found in liver and much lower amount in other organs. Administration of this drug to pregnant or lactating rats showed that a very limited amount passed placenta but appreciable amount secreted in milk. By both oral and i.v. routes, at 24 and 48h, concentrations of radioactivity decreased with discernible low levels being found in large intestine, fat and liver. In mice, oral absorption rate was 30%, while bioavailability is far below this value because of the first-pass effect.

Within 2 hours following an i.v. or i.t dose of [¹⁴C]-ciclesonide to rats, plasma radioactivity consisted of numerous metabolites in addition to unchanged ciclesonide and M1 (B9207-021). In tissues (lung, liver, kidneys) metabolite M1 was the major carrier of radioactivity regardless of route of administration. Unchanged parent compound was only present in small amount.

Repeat inhalation exposure in rats for 2 years and dogs for 3 months were reported. In both of the two studies, drug exposures as assessed by Cmax and /or AUC were proportional to the dose administered. No drug accumulation was observed over the study period. In the dog study, the methods of aerosol generation, MDI versus DPI, were compared. AUC was not influenced by the method of aerosol generation. However, Cmax was higher following inhalation of aerosol generated from a MDI.

TOXICOLOGY

Toxicity of Ciclesonide in beagle dogs following inhalation as powder aerosol/as MDI generated aerosol for 3 months

Background information: The following inhalation Studies have been submitted: 4-week in rats (DPI and MDI with HFA), dogs (DPI, MDI with both CFC and HFA); 26-week in rats (DPI) and dogs (MDI with CFC); and 52-week in dogs (DPI). The current submission reported a 3-month study in dogs with MDI and DPI formulation to bridging between 12-month study in DPI and MDI (see the meeting minutes for the end of phase II meeting, Oct. 22, 1999). This study is required before conducting the clinical trial longer than 3 months.

Study date: May 28, 1998-Jun. 22, 1999

Vol./page: 6/1

Study No. HD0555

Report No. 273/98

Conducting Lab: Byk Gulden Institute of Pathology and Toxicology

GLP: The report was accompanied with a signed GLP statement.

QA report: Yes.

Drug /lot: Ciclesonide

Formulation/vehicle: Aerosol of powder or MDI containing ethanol and HFA-134a.

Methods: Beagle dogs 4/sex/group (additional 2/sex in the group 4 and 5 for recovery study) were exposed to ciclesonide by inhalation for 30 min, once a day for 3 months. Aerosol concentrations were 2, 7, or 15 µg/l generated by MDI and 15 µg/l generated by DPI. The control animals were exposed to vehicle (—% ethanol and —% HFA134a).

b(4)

Observation and times:

Clinical signs: Daily

Body weights: Day -18, -4, 1, 4, once a week.

Food consumption: Daily.

Ophthalmoscopy: Week -3, -1, 12.

Physical examinations: Week -1, 4, 12 for all animals and week 17 for recovery animal only.

Respiratory function: Week -3 and 12 for all animals and week 17 for recovery animals.

ECG: Week: -2, -1, 4, 13, 17.

Hematology: Week -2,-1, 4, 13 for all animals and week 17 for recovery animals.

Serum chemistry: At the same time as hematology.

Urinalysis: Week 13 for all and week 17 for recovery animals.

Toxicokinetics: Day 1 and during week 13 at pre-exposure, as well as 0.5, 1, 1.5, 2, 3, 4, and 6h post-exposure.

Cortisol serum determination: Week -2 and -1 at 10 hr after exposure; week 1, 4, 13, and 17 at 9 hr after exposure.

Organ weights: At necropsy: heart, liver, kidney, brain, thyroid, adrenals, pancreas, testes, ovaries, uterus, spleen, lungs, and prostate.

Histopathology: A complete histopathology battery was covered except a few organs (see addendum for histopathology inventory on page 17).

Results:

Drug exposure: The mass median aerodynamic diameter during the entire test period was in the range of ————. The inhaled doses were 15, 53, and 111 µg/kg using MDI and 113 µg/kg using DPI assuming a respiratory minute volume of 5 l/min, a body weight of 10 kg and a deposition factor of 0.5.

b(4)

Clinical signs: No substance-related observations were noted.

Mortality: None.

Body weight: No substance-related changes in body weight.

Food consumption: No toxicological significant findings.

Physical examination: No substance-related findings.

Respiratory function: Not influenced by aerosol treatment.

ECG: Not influenced by test substance treatment.

Ophthalmoscopy: No substance-related findings.

Hematology: No substance-related findings.

Serum chemistry: Compared to control, dose-related increases of serum cholesterol levels were seen in both sexes at 13 weeks of dosing with MDI (σ , \uparrow 14-31%; ♀ , \uparrow 21-44%). DPI treatment for 13 weeks showed similar changes (σ , \uparrow 16%; ♀ , \uparrow 44%). Increases of cholesterol levels were also observed at week 4 with MDI treatment although less clear dose relationship was seen.

Cortisol levels: Serum cortisol levels decrease were only seen in animals with high dose (55.5 $\mu\text{g}/\text{kg}$ by MDI and 56.5 $\mu\text{g}/\text{kg}$ by DPI) ciclesonide. The decrease were started in week 4 with some individual variability (σ , MDI \downarrow 75%, DPI \downarrow 92%; ♀ , MDI \downarrow 74%, DPI \downarrow 57% compared to control) and seen in almost all HD animals in week 13 (σ , MDI \downarrow 87%, DPI \downarrow 99%; ♀ , MDI \downarrow 76%, DPI \downarrow 55%). All recovery animals showed normal cortisol levels upon withdrawal of test substance for 4 weeks.

Urinalysis: No substance-related findings.

Toxicokinetics:

For the parent compound, B9207-015, AUC and T_{1/2} was not obtained due to a trend of increased blood concentrations at later timepoints with unknown reasons. C_{max} were presented table 1. For the metabolite, B9207-021, TK parameters are shown in table 2. Drug exposure as assessed by C_{max} of B9207-015 and B9207-021 as well as AUC of B9207-021 were proportional to the dose and remained relatively constant throughout the study. The AUC of B9207-021 were independent of method of aerosol generation. However, C_{max} values of B9207-015 and B9207-021 were higher following inhalation of aerosol generated from a MDI.

Table 1. PK parameters of B9207-015 in dogs

Group	Dose in inhaled air ($\mu\text{g}/\text{l}$)	Day 1		Day 87	
		C _{max} ($\mu\text{g}/\text{l}$)	T _{max} (h)	C _{max} ($\mu\text{g}/\text{l}$)	T _{max} (h)
2 (MDI)	2	1.321	0.5	1.279	0.5
3 (MDI)	7	4.490		3.930	
4 (MDI)	15	9.174		8.742	
5 (powder)	15	5.706		4.252	

Table 2. PK parameters of B9207-021 in dogs.

Group	Dose*	Day 1				Day 87			
		C _{max}	AUC _(0,inf)	T _{max}	T _{1/2} **	C _{max}	AUC _(0, 24)	T _{max}	T _{1/2} **
2 (MDI)	2	0.760	1.56	0.81	2.29	0.733	2.09	1.00	2.80
3 (MDI)	7	2.449	4.91	0.75	1.72	1.986	5.18	0.94	1.70
4 (MDI)	15	6.089	15.49	0.94	4.02	5.177	15.92	1.00	5.96
5(powder)	15	3.570	16.54	1.38	4.04	3.212	16.36	1.13	5.59

Unit for PK parameters: C_{max}, µg/l; AUC, µg.h/l; T_{max}, h. * target concentration of B9207-015 in inhaled air (µg/l), **, estimated up to 24 h for group 4 and 5.

Organ weights: Adrenal weights were reduced in both sexes in dose-related manner without regard to aerosol generation with MDI or DPI (♂ HD ↓ 47-59%; ♀ HD ↓ 35-37%).

Histopathology:

Major changes were typical glucocorticoid like effects. These effects were adrenal cortical atrophy, lymphoid organ suppressions (increased severity of thymic atrophy, decrease of spleen follicle size and numbers, as well as decrease of secondary follicles size and numbers in lymph nodes), increase of fat in bone marrow, as well as skin hair follicle regression. Disturbances of reproductive cell generation in both sexes may also were noted and may be related to steroid effects. The changes less associated with steroid effects were the findings in liver: low grade of centrilobular hypertrophy, single ballooned cells and cytoplasmatic eosinophilic inclusions. Additionally, direct effects in respiratory system were also observed including emphysema, bronchiolar distension, and alveolitis. All of these histopathological changes were seen at the HD, and most of the changes were dose-related.

No difference between MDI and DPI were noted in histopathology study.

APPEARS THIS WAY ON ORIGINAL

The following table shows the incidences of histopathological changes described above.

Group	Males							Females						
	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Adrenal cortical atrophy	0/4	2/4	3/4	4/4	4/4	1/2	2/2	0/4	0/4	4/4	4/4	4/4	2/2	1/2
Liver														
Centrilob. Hypertrophy	0/4	2/4	2/3	1/4	3/4	0/2	1/2	0/4	4/4	3/4	3/4	4/4	0/2	1/2
Cytoplasmatic inclusion	0/4	0/4	0/3	0/4	1/4	0/2	0/2	0/4	0/4	0/4	1/4	1/4	0/2	0/2
Ballooned cells	0/4	0/4	0/3	1/4	2/4	0/2	0/2	0/4	0/4	0/4	1/4	0/4	0/2	0/2
Fat deposition in kupffer's	0/4	NE	NE	3/4	2/4	NE	NE	2/4	NE	NE	3/4	2/4	NE	NE
Fat dep. in single cells	0/4	NE	NE	0/4	1/4	NE	NE	0/4	NE	NE	1/4	0/4	NE	NE
Diffused fat deposition	0/4	NE	NE	1/4	0/4	NE	NE	0/4	NE	NE	0/4	0/4	NE	NE
Lung														
Emphysema	0/4	NE	1/1	1/4	2/4	NE	NE	0/4	0/1	0/1	2/4	2/4	NE	NE
Alveolitis	0/4	NE	1/1	3/4	3/4	NE	NE	0/4	0/1	0/1	1/4	1/4	NE	NE
Bronchiolar distension	0/4	NE	1/1	1/4	4/4	NE	NE	0/4	0/1	0/1	3/4	2/4	NE	NE
Lymph node follicle decrease	0/4	NE	NE	4/4	4/4	NE	NE	0/4	NE	NE	3/4	2/4	NE	NE
Spleen follicular atrophy	0/4	0/4	1/4	2/4	4/4	0/2	0/2	0/4	2/4	4/4	4/4	4/4	0/2	1/1
Thymic atrophy	3/4	4/4	4/4	4/4	4/4	0/2	0/2	3/4	¼	4/4	4/4	4/4	0/2	0/2
Fatty bone marrow	0/4	NE	NE	0/4	3/4	NE	NE	0/4	NE	NE	1/4	0/4	NE	NE
Testes sperminogenic disturbance	0/4	NE	NE	1/4	0/4	NE	NE							
Testes tubular degeneration	0/4	NE	NE	1/4	0/4	NE	NE							
Ovary follicular atresia								0/4	NE	0/1	1/4	3/4	NE	NE
Skin hair follicle regression	0/4	NE	NE	0/4	3/4	NE	NE	0/4	NE	NE	3/4	1/4	NE	NE

Group 1, 2, 3, 4, 5, 6 and 7 represent control, MDI 15µg/kg, MDI 53 µg/kg, MDI 111 µg/kg, DPI 113 µg/kg, MDI 111 µg/kg recovery, and DPI 113 µg/kg recovery group, respectively; NE, not examined.

Conclusions:

Three month study with ciclesonide in dogs at doses of 15, 53 and 111 µg/kg in MDI and 113 µg/kg in DPI were reported. Plasma AUC was not influenced by the method of aerosol generation. Cmax was higher following inhalation of aerosol generated from MDI. In spite of this variation, no difference in toxicity was observed between treatment of aerosol generated from MDI and DPI.

Major adverse effects of ciclesonide were glucocorticoid like compound effects. These effects included suppression of adrenal gland and lymphoreticular tissues, disturbance in reproductive cell generation, as well as increase fat amount in bone marrow and fat deposition in liver. Other adverse effects were less relevant to glucocorticoid effects including changes in liver (centrilobular hypertrophy, eosinophilic cytoplasic inclusion, ballooned cells) and lung (emphysema, alveolitis, bronchiolar distension).

The NOAEL was 15 µg/kg, a dose that produced mild, tolerable, expected glucocorticoid effects.

Histopathology inventory for IND 62,739

Study	273/98		
Duration of treatment	3 mon		
Species	Dog		
Adrenals	X*		
Aorta	X		
Bone Marrow smear	X		
Bone (sternum)	X		
Brain	X*		
Cecum	X		
Cervix			
Colon	X		
Duodenum	X		
Epididymis	X		
Esophagus	X		
Eye	X		
Fallopian tube			
Gall bladder			
Gross lesions			
Harderian gland			
Heart	X*		
Ileum	X		
Injection site			
Jejunum	X		
Kidneys	X*		
Lachrymal gland			
Larynx			
Liver	X*		
Lungs	X*		
Lymph nodes, cervical	X		
Lymph nodes mandibular			
Lymph nodes, mesenteric	X		
Mammary Gland	X		
Mesenteric Blood vessels			
Nasal cavity	X		
Optic nerves			
Ovaries	X*		
Pancreas	X*		
Parathyroid	X		
Peripheral nerve			
Pharynx			
Pituitary	X		
Prostate	X*		
Rectum	X		
Salivary gland	X		
Sciatic nerve	X		
Seminal vesicles			
Skeletal muscle	X		
Skin	X		
Spinal cord	X		
Spleen	X*		
Sternum			
Stomach	X		
Testes	X		
Thymus	X		
Thyroid	X*		
Tongue	X		
Trachea	X		
Urinary bladder	X		
Uterus	X*		
Vagina	X		
Zymbal gland			

X, histopathology performed, * organ weight obtained.

Reverse Mutation Test of Ciclesonide in Bacteria

Study date: Jan. 16, 1998 –Jun. 04, 1998

Vol./page: 5/347

Study No. S065M0B900

Report No. 44E/99

Conducting Lab: Teijin Institute for Biomedical Research, Japan

GLP: No statement attached.

QA report: Not signed.

Drug lot: MS690/C

Study Endpoint: Bacterial mutation (Salmonella, E. coli)

Methods:

Strain/Species/Cell line: Salmonella TA1535, TA1537, TA98, TA100
E. coli WP2 uvrA

Test method: Pre-incubation method

Dose selection Criteria:

Basis of dose selection: Test limit of 5 mg/plate

Range finding studies: Eight concentrations from 39 to 5000 µg/plate were tested in duplicate plate (negative control in triplicate), ±S9, for each strain. No cytotoxicity was observed in any strain regardless of presence or absence of S9. The revertant colony count of TA1537 at 2500 µg/plate in absence of S9 was about twice that of the negative control, dose-dependent increase was not observed. No increase of revertant colony was observed in other strains, regardless of presence or absence of S9 and also did not increase dose-dependently. Precipitation of test compound was seen in experiments with each strain at 78µg/plate and higher without S9 and at 625 µg/plate and higher with S9.

Test agent stability: Drug solution made freshly and used within 3 hr; stability not tested.

Metabolic activation: S9 from male SD rats treated with phenobarbital (PB) and 5,6-Benzoflavone (BF).

Controls:

Vehicle: DMSO

Positive Controls:

Strain	Without S9(µg/plate)	With S9(µg/plate)
Salmonella TA98	AF-2 (0.1)	2-anthramine (0.5)
Salmonella TA1537	ICR-191 (1)	2-anthramine (2)
Salmonella TA100	AF-2 (0.01)	2-anthramine (1)
Salmonella TA1535	ENNG (5)	2-anthramine (2)
E. coli WP2 uvrA	AF-2 (0.01)	2-anthramine (20)

AF-2: 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide, ICR-191: ICR-191 Acridine Mutagen Dihydrochloride, ENNG: N-Ethyl-N'-nitrosoguanidine

Exposure conditions:

Incubation and sampling times: Incubated for 48 hours at 37°C before counting colonies.
Dose used in definitive study: 2.4, 4.9, 9.8, 20, 39, 78, 156 µg/plate for all strains ± S9.

Analysis:

Number of plates analyzed: Duplicate plate per dose of test compound, and triplicate plate of negative control.

Counting method: manual counting

Cytotoxicity endpoints: decrease background lawn or revertant colonies.

Genetic toxicity endpoints: Number of revertant colonies/plate

Statistical methods: None

Criteria for positive results: Dose-related increase of revertant colony count at one or more doses to twice or more that of negative control.

Results:

Study validity: Vehicle and positive controls were within historic ranges. The 5 mg/plate dose limit is appropriate.

Study Outcome: The study was repeated twice and observed the similar results.

Precipitation was seen at dose 78 µg/plate and 156 µg/plate. All dosed plates were counted for revertant colonies. Ciclesonide did not increase revertant colonies compared to solvent controls under any of the test conditions.

Conclusion:

Ciclesonide does not induce mutation either directly or with metabolic activation in Salmonella or E. coli strains.

SPECIAL TOXICITY

Immunostimulation

Study date: Jan. 1998-July 1998

Vol./page: 10/73

Study No. SO65HOG300

Report No. 48E/99

Conducting Lab: Teijin Institute of Biomedical Research, Japan

GLP: No signed GLP compliance statement.

QA report: QA report was not signed.

Drug /lot: Ciclesonide/MS690/C

Formulation/vehicle: Ciclesonide dissolved in ethanol and propylene glycol.

Methods:

Guinea pigs were sensitized by injection with antigen mixed with FCA subcutaneously once a week for 3 weeks. The half animals of each group were used for ASA (active

systemic anaphylaxis) and remained half animals were used for PCA (passive cutaneous anaphylaxis). ASA was conducted as the follows: 2 weeks after the last dose of sensitization, animals were intravenously injected with antigen solution and evaluated for anaphylaxis symptoms 30 minutes after the challenge. For PCA test, the passive sensitization was conducted as follows: sera were collected from guinea pigs 13 days after the last sensitization. After a series of dilution, each animal's sera were injected to two intact guinea pigs' dorsal skin. These recipients were, 4 hr later, i.v. injected with Evans Blue followed by injection of challenge antigen solution. Evaluation was performed 30 min after challenge by measuring the size of blue spot on the back.

Results:

ciclesonide showed negative results in ASA and PCA reaction. Positive controls in both tests showed typical positive reactions.

ASA reaction:

Group	Sensitizing Ag	Challenging Ag	N	General Score*			
				-	±	+	++
1	Ciclesonide 5µg/kg + FCA, s.c	Ciclesonide 50µg/kg, i.v.	6	6	0	0	0
2	Ciclesonide 50µg/kg + FCA, s.c	Ciclesonide 50µg/kg, i.v.	6	6	0	0	0
3	DNP-Alb 10 mg/kg + FCA, s.c	DNP-Alb 10 mg/kg, i.v.	6	0	0	0	6
4	Vehicle + FCA, s.c.	Ciclesonide 50µg/kg, i.v.	6	6	0	0	0

General score: -: no sign, ±: licking nose ruffling fur, +: Tremor, cough, cyanosis, upset, ++: Positive (death)

PCA reaction:

Group	Sensitizing Ag	Challenging Ag	N	PCA reaction		PCA titer
				+	-	
1	Ciclesonide 5µg/kg + FCA, s.c	Ciclesonide 50µg/kg, i.v.	6	0	6	<5
2	Ciclesonide 50µg/kg + FCA, s.c	Ciclesonide 50µg/kg, i.v.	6	0	6	<5
3	DNP-Alb 10 mg/kg + FCA, s.c	DNP-Alb 10 mg/kg, i.v.	6	6	0	≥3200
4	Vehicle + FCA, s.c.	Ciclesonide 50µg/kg, i.v.	6	0	6	<5

Conclusions:

Under the test condition, ciclesonide caused no anaphylactic symptoms or passive cutaneous anaphylactic reaction in guinea pigs at dose up to 50 µg/kg.

Antigenicity study of Ciclesonide in mice-rats (PCA reaction)

Study date: Jan. 1998-July 1998

Vol./page: 10/95

Study No. SO65HOM300

Report No. 49E/99

Conducting Lab: Teijin Institute of Biomedical Research, Japan

GLP: No signed GLP compliance statement.

QA report: QA report was not signed.

Drug /lot: Ciclesonide/MS690/C

Formulation/vehicle: Ciclesonide dissolved in ethanol and propylene glycol.

Methods:

Male mice (10/group) were i.p. injected with sensitizing antigen twice at interval of 4 weeks. Sera of these sensitized mice were collected 2 weeks after the end of sensitization. The individual sera were diluted in a 2-fold series and 50 µl of the diluted sera were injected intradermally into the dorsal skin of a recipient of each corresponding group. A pair of two intact rats was used as recipient in each sera. Evan Blue and challenge antigen was injected intravenously 24h after passive sensitization. Evaluation was performed 30 min after injection of challenging antigen by measuring the size of blue spots at the intradermal injection site.

Results:

A mouse of the 2nd group died after the 2nd sensitization.

Animal injected with sera from ciclesonide sensitized (5, 50 µg/kg+Alum) animals showed negative PCA response upon challenge with ciclesonide, and the antibody titer was <5. On the other hand, positive control, OVA, showed the effect of antigenicity with antibody titers of 200-800.

The result of PCA is shown in the table below.

Group	Sensitizing Ag	Challenging Ag	N	PCA Reaction		PCA titer
1	Ciclesonide 5µg/kg + Alum, i.p.	Ciclesonide 50µg/kg i.v.	10	0	10	<5
2	Ciclesonide 50µg/kg + Alum, i.p.	Ciclesonide 50µg/kg i.v.	9	0	9	<5
3	OVA + Alum	OVA 10 mg/kg, i.v.	10	10	0	200-800
4	Vehicle +Alum	Ciclesonide 50µg/kg i.v.	10	0	10	<5

Alum: aluminum hydroxide gel suspension.

Conclusions: Ciclesonide is negative in mice-rats PCA reaction.

OVERALL SUMMARY AND EVALUATION

The current submission includes four aspects of data: in vitro pharmacology, ADME in vitro as well as in vivo, toxicity study in dogs for 3 months and special toxicity studies (hypersensitivity studies).

The metabolite (M1) of the R-epimer of Ciclesonide inhibited the CD3-induced proliferation of human PBMC and was as potent as Budesonide, but less potent than Fluticasonepropionate, Rofleponide and Mometasonefuroate. In vitro glucocorticoid receptor binding assay showed that M1 had the similar binding affinity as Budesonide that was higher in comparison with dexamethasone. The binding affinity of metabolites of M1 (B9207-021), M2, M3a and M5 was lower than M1.

In vitro metabolism studies showed that glucuronidation occurred when B9207-021 was cultured with dog liver slices. Incubation with dog microsomal fraction resulted in more intensive metabolism than with cytosolic fraction.

In mouse circulation, ciclesonide and its active metabolite, B9207-021, were rapidly (T_{1/2} of 1.8 h) converted to other metabolites. In tissues (lungs, liver and kidneys), M1 was the major carrier of radioactivity and ciclesonide was only present in small amounts, suggesting pronounced esterase was present in tissues. Oral absorption of ciclesonide in mice was about 30%. However bioavailability was far lower than 30% due to the first pass effect. Repeat inhalation for 2 years in rats and 3 months in dogs showed that drug exposure (C_{max} and/or AUC), was approximately in proportion to the dose. No plasma accumulation occurred over the study period. No sex-associated differences were observed. When compared with DPI, MDI provided the same AUC but higher C_{max} in dogs.

[¹⁴C]-ciclesonide given by i.v. to rats showed that the drug distributed to lung, myocardium, followed by intestinal content, liver, and salivary glands and fat. Oral dose was moderately absorbed and mainly distributed to liver and much lower amount in other organs.

The dog 3-month inhalation study showed there was no significant difference between the treatment aerosol generated from MDI and DPI regarding to AUC and toxicity. The higher level of C_{max} following MDI treatment did not seem to have an influence on toxicity. Major adverse effects of ciclesonide were glucocorticoid-like compound effects. These effects included suppression of adrenal gland and lymphoreticular tissues, disturbance in reproductive cell generation, as well as increase in fat amount in bone marrow and fat deposition in liver. Other adverse effects were less relevant to glucocorticoid effects including changes in liver (centrilobular hypertrophy, eosinophilic cytoplasmic inclusion, ballooned cells) and lung (emphysema, alveolitis, bronchiolar distension). The NOAEL was 15 µg/kg, a dose that produced mild, tolerable, expected glucocorticoid effects.

Ciclesonide was negative in an Ames test.

After an oral or intravenous dose of [¹⁴C]-ciclesonide to pregnant rats, high radioactivity was seen in maternal liver, lungs, adrenal and kidneys. Very limited amount passed placenta. Appreciable amount of ciclesonide or its metabolites was secreted in milk.

Additionally, ciclesonide caused no anaphylactic symptoms or passive cutaneous anaphylactic reaction in guinea pigs at dose up to 50 µg/kg and was negative in mice-rats PCA reaction.

After reviewing previous submission, it is noted that the NOAEL in 12-month dog DPI inhalation study has not been established although the issue of nasal trabecular osteofibrosis and thickening has been resolved (review 6, Mark Vogel, Mar. 1, 1999).

The findings of spermiogenic disturbance in all dose levels (LD 2/4, MD 3/4, HD 1/4, recovery 1/2) in this 12-month study raises a safety concern. Additionally, in the 3-month dog MDI and DPI inhalation study, spermiogenic disturbance was observed in 1/4 at HD (MDI). There was no detail description of this pathological change provided in either 12-month study report or 3-month study report. Furthermore, no individual data were provided in the 12-month study. The sponsor should be asked to submit line listings for the 12-month study and explain these pathological changes. In the absence of NOAEL in 12-month dog inhalation study, clinical trial is approved for up to 3 month (see the meeting minutes after end of phase II meeting on Nov. 17, 1999).

Recommendation:

As described above, the sponsor should be asked to submit individual data for the 12-month dog DPI study, explain the pathological changes of spermiogenic disturbance and toxicological consequence, and provide relevant historic control data.

Draft letter to the sponsor:

b(5)

Huiqing Hao, Ph.D. Pharmacologist

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/s/

Huiqing Hao
12/12/01 01:57:57 PM
PHARMACOLOGIST

Joseph Sun
12/12/01 05:31:33 PM
PHARMACOLOGIST
I concur.

ATTACHMENT 8.

**HFD-570 DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION**

Review 9

IND number: 53,391

Serial No. N-140-IT

Date of submission: 05/10/02.

Reviewer: Huiqing Hao, Ph.D.

Review Completion Date: 05/29/01

Communication to Sponsor: Yes (X) No ()

Sponsor: Byk Gulden Lomberg Chemische Fabrik GmbH, Germany

Drug: Ciclesonide (Active ingredient B9207-015)

Relevant INDs/NDAs/DMFs: None.

Drug class: Glucocorticoid Steroid

Indication: Asthma

Route of administration: Oral Inhalation (MDI)

Clinical Formulation: MDI with HFA-134a propellant and 9.7% ethanol

Proposed clinical dose and duration: Phase III, up to 800 µg/day for 12 weeks and one year in adults, and up to 200 µg/day for 12 weeks and one year in children.

Background: It was noticed that no individual data were provided in the previous report of the 52-week dog inhalation study (submitted on Mar. 23, 1997, study report No. 116/96). Histopathological changes of spermiogenic disturbance were observed at all dose-levels. A request for individual data, its toxicological consequence and historic control data was sent to the sponsor on Mar. 7, 2002 (review 8, Huiqing Hao). The sponsor responded to the Division's request in the current submission.

Studies reviewed in this submission:

Toxicity of B9207-015 in beagle dogs following inhalation for 12 months (study report No.116/96, line lists were included).

Studies not reviewed in this submission: None.

Evaluation:

The study report contained line-listing data, but no detail description for the spermiogenic disturbance. The following table lists the incidence of findings in testes.

Dose (µg/kg)	0	18	47	92	92-0*
Tubular degeneration	2/4	2/4	2/4	2/4	0/2
Atrophy	0/4	0/4	1/4	0/4	0/2
Spermiogenic disturbance	0/4	2/4	3/4	1/4	1/2
Giant cells	0/4	1/4	1/4	0/4	0/2
Tubular shrinkage	2/4	4/4	2/4	1/4	1/2

* Autopsied after a 4 week recovery period.

b(4)

The sponsor explained that the finding of spermiogenic disturbance represents effects attributed to poor fixation and/or handling of specimens during tissue preparation. The morphological features of the finding original described by the Study Pathologist were similar to those described in a published paper by Rehm (Toxicol pathol 28:782-787, 2000): cytoplasmic rarefaction, poor staining, disruption of germ cell layers, sloughing of normal germ cells, piling of cells in the lumen and tubular shrinkage. The sponsor, therefore, concluded that it has no toxicological significance and no historic data is necessary to submit.

This artifact nature of the original findings is possible. However, the absence of "spermiogenic disturbance" in the control group does not support this explanation. Additionally, the finding of spermiogenic disturbance in the high dose group (1/4) of ciclesonide (in HFA) but not other groups, in the 3-month dog study (Report # 273/98) does not support this explanation either.

Recommendation: The sponsor should be asked to provide historic control for the artifact of "spermiogenic disturbance" and explain its toxicological consequence.

Draft letter to the sponsor:

b(5)

Huiqing Hao, Ph.D., Pharmacologist

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/s/

Huiqing Hao
5/29/02 02:29:24 PM
PHARMACOLOGIST

Joseph Sun
5/29/02 04:21:09 PM
PHARMACOLOGIST
I concur.

ATTACHMENT 9.

HFD-570 DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

Review 13

IND number: 53,391

Serial No. N-184 IT

Date of submission: 04/21/2003

Reviewer: Huiqing Hao, Ph.D.

Review Completion Date: 05/06/2003

Communication to Sponsor: Yes (X) No ()

Sponsor: Aventis Pharmaceuticals

Drug: Ciclesonide (Active ingredient B9207-015)

Relevant INDs/NDAs/DMFs: None.

Drug class: Glucocorticoid Steroid

Indication: Asthma

Route of administration: Oral Inhalation (MDI)

Proposed clinical dose and duration: None at this time.

Study reviewed in this submission: Pathology working group report on dog testes.

Background: Spermio-genic disturbance was reported in a 3-month and a 12-month dog inhalation study and the sponsor was requested to provide historical control data (review 9, Huiqing Hao, 05/29/2002). In the pre-NDA meeting on 08/29/2002, the sponsor indicated that there is no historical data to provide and proposed to invite an independent pathology panel to re-evaluate the tissue slides. The current submission provided such report from the pathology-working group.

Evaluations:

The tissue slides were re-evaluated by a Reviewing Pathologist. Based on the results of the Reviewing Pathologist and original study Pathologist's diagnoses, Pathology Working Group (PWG) chairperson decided which slides were to be reviewed in a coded fashion by the PWG panel of pathologists.

PWG's diagnoses were artifacts, not remarkable or tubular degeneration for the slides from 5 dog Ciclesonide studies that were previously reported with spermio-genic disturbance. The following tables present the incidences of the findings reported by the original pathologist and the PWG (the incidences of non-remarkable findings are not included in the tables).

12-month oral Ciclesonide study (CD0479) in dogs

Dose (mcg/kg)	Animal n	Study pathologist's diagnosis (original)		PWG's diagnosis (new)	
		Spermi. Dist.	Tubular degen.	Tubular degen.	Artifact
0	5	0/5	2/5	2/5	2/5
5	5	1/5	0/5	1/5	1/5
30	5	5/5	0/5	1/5	4/5
200	5	5/5	0/5	1/5	3/5
200-0	2	1/2	½	1/2	1/2

12-month Ciclesonide inhalation study in dogs (HD0356)

Dose (mg/kg)	Animal n	Original pathologist's diagnosis		PWG's diagnosis	
		Spermi. Dist.	Tubular degen.	Tubular degen.	Artifact
0	4	0/4	¼	2/4	4/4
18	4	2/4	2/4	¼	4/4
47	4	¾	2/4	¾	4/4
92	4	¼	2/4	0/4	4/4
92-0	2	½	0/2	0/2	2/2

4-week oral Ciclesonide study in dogs (BD0270)

Dose (mcg/kg)	Animal n	Original pathologist's diagnosis		PWG's diagnosis	
		Spermi. Dist.	Tubular degen.	Tubular degen.	Artifact
0	3	0/3	2/3	3/3	3/3
10	3	0/3	0/3	NE	NE
40	3	1/3	2/3	0/1	0/1
400	3	1/3	1/3	0/1	1/1
400-0	2	1/2	0/2	1/1	1/1

4-week Ciclesonide inhalation study in dogs (HD0459)

Dose (mcg/kg)	Animal n	Original pathologist's diagnosis		PWG's diagnosis	
		Spermi. Dist.	Tubular degen.	Tubular degen.	Artifact
0	4	0/4	0/4	0/4	2/4
2	4	0/4	0/4	1/1	1/1
7	4	0/4	0/4	0/2	2/2
15	4	0/4	¼	NE	NE
15-0	4	2/4	0/4	0/2	0/2

3-month Ciclesonide inhalation study in dogs (HD055)

Dose (mcg/kg)	Animal n	Original pathologist's diagnosis		PWG's diagnosis	
		Spermi. Dist.	Tubular degen.	Tubular degen.	Artifact
0	4	0/4	0/4	0/4	4/4
2 (MDI)	4	NE	NE	NE	NE
7 (MDI)	4	NE	NE	NE	NE
15 (MDI)	4	1/4	¼	0/1	1/1
15(DPI)	4	0/4	0/4	1/1	1/1
15-0 (MDI)	2	NE	NE	NE	NE
15-0 (DPI)	2	NE	NE	NE	NE

Additionally, dysspermia was used as synonym for spermiogenic disturbance by the original sponsor (Byk Gulden). PWG re-evaluated the tissue slides from a dog ciclesonide study (4 week MDI) with the previous reports of dysspermia and concluded that they were artifacts, not remarkable or tubular degeneration. The comparison of the positive findings reported by the original pathologist and the current PWG is presented in the table below.

4-week MDI Ciclesonide inhalation study in dogs (HD493)

Dose (mcg/kg)	Animal n	Original pathologist's diagnosis		PWG's diagnosis	
		Dysspermia	Tubular degen.	Tubular degen.	Artifact
0	4	0/4	¼	¼	4/4
0.4	4	0/4	0/4	NE	NE
0.8	4	¼	0/4	0/1	1/1
2.5	4	¼	2/4	0/1	1/1
2.5-0	2	0/4	2/2	0/1	1/1

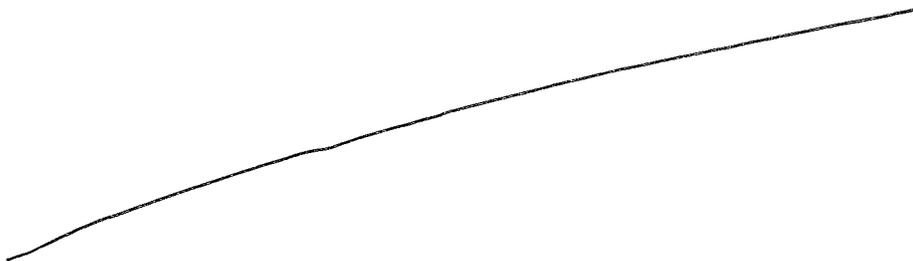
The PWG reported the changes initially reported by the Study Pathologist as spermiogenic disturbance or dysspermia represent artifacts due to suboptimal tissue fixation or handling during necropsy. They further stated that these artifacts were seen in controls and treated dogs in each of the studies. Therefore, the original findings of spermiogenic disturbance or dysspermia have not toxicological significance.

However, as shown in the above tables, none of the control animals in the six studies was observed with spermiogenic disturbance or dysspermia. In contrast, all of animals reported with such findings were Ciclesonide treated. The PWG's explanation of artifact for "spermiogenic disturbance or dysspermia" does not seem to compatible with this observation. PWG's re-evaluation is not quite convincing to relieve our safety concern for this issue.

Recommendations:

The sponsor should be requested to explain the reason for lack of historical control data for beagle dog spermiogenic disturbance as they stated in the pre-NDA meeting. Since no animal data is available to clarify the clinical relevance for these findings, clinical monitoring for male spermiogenesis may be placed in clinical trials.

Draft letter to the sponsor:



b(5)

Huiqing Hao, Ph. D., Pharmacologist

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/s/

Huiqing Hao
5/7/03 05:19:25 PM
PHARMACOLOGIST

Joseph Sun
5/8/03 05:20:51 PM
PHARMACOLOGIST
I concur.

ATTACHMENT 10.

**HFD-570 DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION**

Review 12

IND/NDA number: IND 53391

Date of submission: 08/15/2002

Series number: N-155

Reviewer: Huiqing Hao, Ph.D.

Review Completion Date: 05/24/2003

Communication to Sponsor: Yes () No (X)

Sponsor: Aventis

Drug: Ciclesonide MDI

Code name: B9207-015

Relevant INDs/NDAs/DMFs: None

Drug class: Glucocorticoid steroid.

Indication: Asthma

Route of administration: Oral inhalation

Clinical Formulation: MDI that delivers ciclesonide — 100 and 200 µg (ex valve) per puff with — 6 (w/w) propellant HFA-134a and — (w/w) ethanol.

Proposed Clinical Protocol: NA.

b(4)

Studies reviewed in this submission:

1. B9207-015 (Ciclesonide) – Carcinogenicity study by oral gavage administration to B6C3F1 mice for 104 weeks-Byk Gulden study 281/2000.
2. Toxicokinetics of Ciclesonide in an oral carcinogenicity study in mice –Byk Gulden study 282/2000.
3. Carcinogenicity inhalation study of B9207-015 in metered dose inhaler (MDI) in Wistar (WU) rats-Byk Gulden study 176/99.
4. Toxicokinetics of Ciclesonide in an inhalative carcinogenicity study in Wistar rats (aerosol generated from metered dose inhalers)-Byk Gulden study 177-99.

Studies not reviewed in this submission: None

CARCINOGENICITY

B9207-015 (Ciclesonide) -Carcinogenicity Study by oral gavage administration to B6C3F1 mice for 104 weeks

Toxicokinetics of Ciclesonide in an oral Carcinogenicity Study in mice

Study report #: Byk Gulden study #: main study, 281/2000; TK study, 282/2000.

Volume #: Main study 50.6- 50.9, TK study 50.10.

Conducting Lab. and location: The main study: _____

_____, Byk

b(4)

Gulden Pharmaceuticals, Dept. of Pharmacokinetics and Drug
Metabolism performed PK evaluation.

Study period: Main study, 08/17/1998 – 04/18/2002; TK, 08/1998-03/2001.

GLP compliance: Yes.

Quality assurance: Yes.

Drug lot #, and purity: the same batch of drug was used for main study and TK study:
MS470C expires on Jun. 17, 2001, 99% purity.

CAC concurrence: Executive CAC recommended doses of 150, 450 and 900 mcg/kg for
male and female mice (Mark Vogel, July 14, 1998).

Study type: 2 year bioassay

Species/strain: B6C3F1/ \bar{m} BR mouse.

Number/sex/group; age at start of study: 50/sex/dose; 4 weeks old

Animal housing: 1/cage.

Formulation/vehicle: The test compound was dissolved in 100% polyethylene glycol
400 (PEG 400).

Drug stability/homogeneity: 15 days at 4°C (refrigeration). All solutions were prepared
freshly each week and stored at 4°C in the dark during the study.

Methods:

Doses: 150, 450 and 900 mcg/kg at the volume of 4 ml/kg, control animals
received PEG 400 at the same volume.

Basis for dose selection: MTD

Restriction paradigm for dietary restriction studies: N/A

Route of drug administration: Gavage

Frequency of drug administration: Daily for 104 weeks.

Dual controls employed: Untreated control and vehicle control were included

Interim sacrifice: No

Satellite PK or special study groups: 18 mice/sex/dose out of 50 mice/sex/dose
were also used for TK information.

Deviation from original study protocol: Nothing significant

Observations and times:

Clinical signs and mortality: Daily during acclimation period, daily during week 1, twice weekly during Week 2-4, once weekly during Weeks 5 to 13 and once every two weeks from Week 14 onwards. Detailed physical examinations were performed weekly.

All mice killed in extremis, or found dead were subjected to detailed macroscopic examination and where practicable a full spectrum of tissues was preserved in 10% formalin.

Body weight: Week -1, Day 0, weekly for the first 14 weeks and once every 4 weeks thereafter.

Food consumption: Weekly for the first 14 weeks and once every 4 weeks thereafter.

Food conversion efficiency: Food efficiency ratio (body weight gain per unit food consumption) was calculated for the first 14 weeks.

Water consumption: Daily visual appraisal.

Hematology: Blood samples were collected from all animals when they were killed during the study or at termination.

TK: On Days 1, 176, 358 and 729 blood samples of 0.2 ml were collected from 6 mice/sex at predose, 1 and 4 hours post-dose, and different mice were used at each of the three time points.

Gross pathology: At necropsy.

Histopathology: A comprehensive list of tissues (histopathology inventory, pages 20-21) from all animals were examined. All nodules, tissue masses and samples of any macroscopically abnormal tissues were also examined microscopically.

Results:

Mortality:

There were no treatment related effects on the incidence or distribution of deaths between two control groups, between vehicle control and treated groups, or between untreated and treated groups. The following table and figures present the cumulative incidences of deaths and percentage survival during the 104 weeks of treatment period.

TABLE 1
Cumulative incidence and percentage survival

Week	Group and dosage ($\mu\text{g/kg/day}$)									
	1M 0	2M 0	3M 150	4M 450	5M 900	1F 0	2F 0	3F 150	4F 450	5F 900
1 - 4	0/100	0/100	0/100	0/100	0/100	0/100	0/100	0/100	0/100	0/100
5 - 8	0/100	0/100	0/100	0/100	0/100	0/100	0/100	0/100	0/100	0/100
9 - 12	0/100	0/100	0/100	0/100	0/100	0/100	0/100	0/100	0/100	0/100
13 - 16	0/100	1/98	0/100	0/100	0/100	0/100	0/100	0/100	0/100	0/100
17 - 20	0/100	1/98	0/100	0/100	0/100	1/98	0/100	0/100	0/100	0/100
21 - 24	0/100	1/98	0/100	1/98	0/100	1/98	1/98	0/100	0/100	0/100
25 - 28	0/100	1/98	0/100	1/98	0/100	2/96	2/96	0/100	0/100	0/100
29 - 32	0/100	1/98	0/100	1/98	0/100	2/96	2/96	0/100	0/100	0/100
33 - 36	0/100	1/98	0/100	1/98	0/100	2/96	2/96	0/100	0/100	0/100
37 - 40	0/100	1/98	1/98	1/98	0/100	2/96	2/96	0/100	0/100	0/100
41 - 44	0/100	1/98	1/98	2/96	1/98	2/96	2/96	0/100	0/100	1/98
45 - 48	0/100	1/98	1/98	2/96	1/98	3/94	2/96	0/100	0/100	1/98
49 - 52	0/100	1/98	1/98	2/96	1/98	3/94	2/96	0/100	0/100	1/98
53 - 56	0/100	1/98	2/96	2/96	1/98	3/94	3/94	0/100	0/100	1/98
57 - 60	0/100	1/98	3/94	2/96	1/98	3/94	4/92	1/98	1/98	1/98
61 - 64	0/100	1/98	3/94	2/96	1/98	3/94	4/92	1/98	1/98	1/98
65 - 68	1/98	1/98	3/94	2/96	2/96	3/94	4/92	2/96	1/98	1/98
69 - 72	2/96	1/98	3/94	2/96	3/94	4/92	4/92	2/96	1/98	1/98
73 - 76	2/96	1/98	3/94	2/96	4/92	4/92	4/92	2/96	2/96	1/98
77 - 80	2/96	2/96	4/92	2/96	5/90	4/92	4/92	2/96	3/94	2/96
81 - 84	3/94	2/96	4/92	2/96	5/90	4/92	4/92	3/94	4/92	3/94
85 - 88	3/94	2/96	4/92	2/96	6/88	5/90	4/92	3/94	5/90	3/94
89 - 92	4/92	3/94	4/92	2/96	7/86	6/88	5/90	4/92	5/90	3/94
93 - 96	5/90	5/90	4/92	2/96	7/86	6/88	5/90	4/92	5/90	3/94
97-100	6/88	5/90	7/86	2/96	8/84	9/82	8/84	6/88	5/90	5/90
101-104	7/86	7/86	8/84	3/94	8/84	10/80	10/80	8/84	8/84	6/88

Left number is the cumulative mortality incidence

Right number is the percentage survival

At commencement of treatment there were 50M and 50F in each group

FIGURE 1
Kaplan-Meier survival function for males

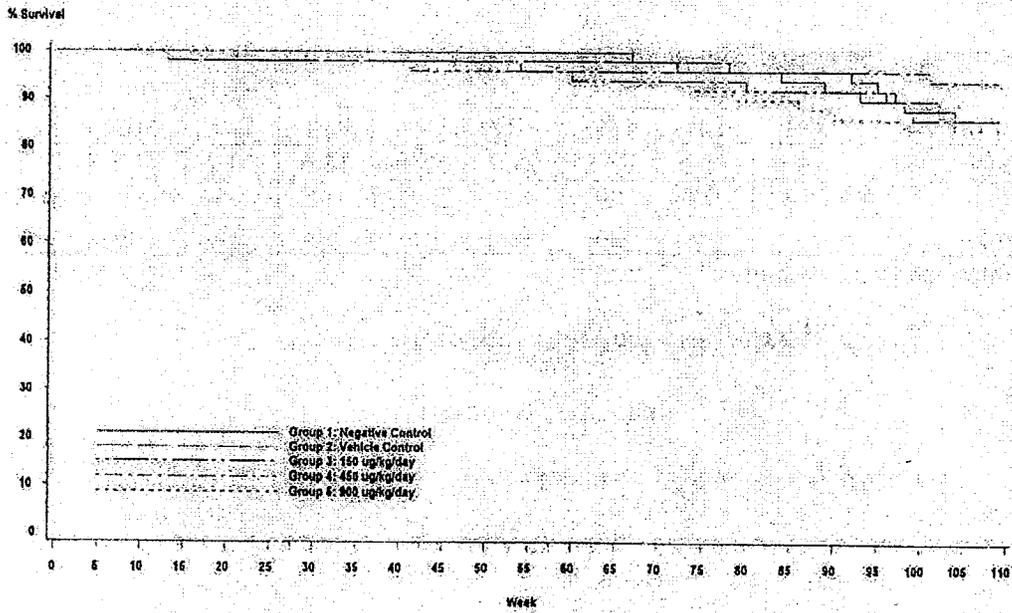
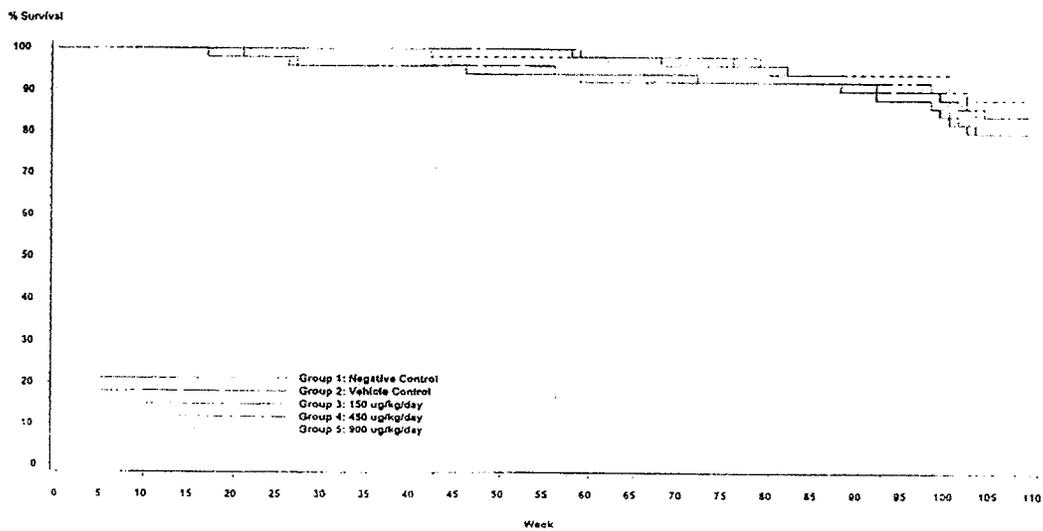


FIGURE 2
Kaplan-Meier survival function for females



Clinical signs:

There were no drug-related findings.

Body weight:

By the end of the 2 years, the body weight was slightly lower at HD and MD (see the table below).

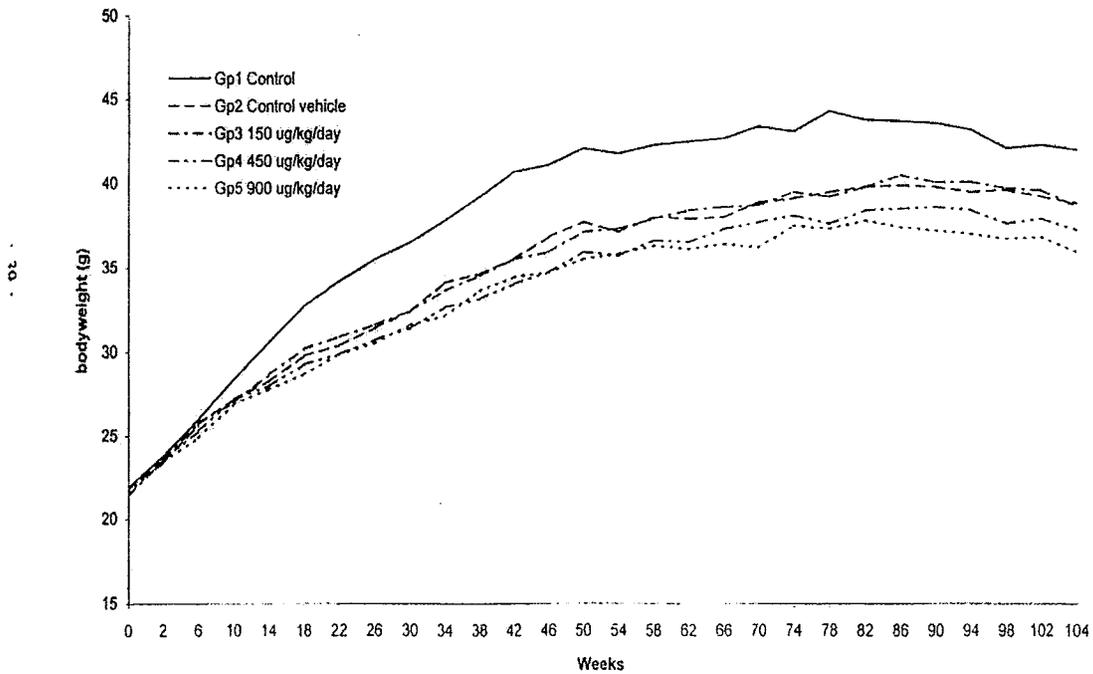
Body weights in the mouse 2-yr study (g)

	Male					Female				
	Unt.	Veh.	LD	MD	HD	Unt.	Veh.	LD	MD	HD
Abs wt (g)	42.0	38.8	38.6	37.2	35.9	35.8	34.6	34.2	34.5	32.5
% of unt.	-	92	92	89	85	-	97	96	96	91
% of veh.	108	-	99	96	93	103	-	99	100	94

unt.=untreated, veh.=vehicle

FIGURE 3

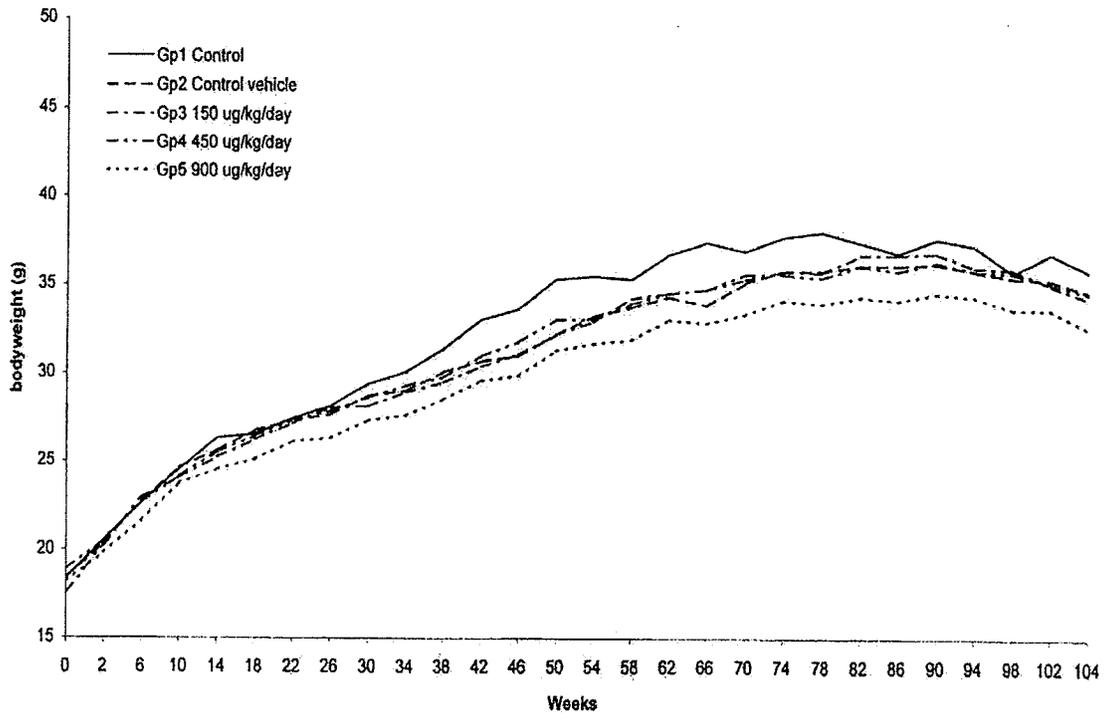
Group mean male bodyweight (g)



BYG 059/012193

FIGURE 4

Group mean female bodyweight (g)



BYG 059/01219

Food consumption: Unaffected by the drug.

Hematology:

There were no drug-related findings. Relative to vehicle control, decrease of lymphocyte counts (σ , $\downarrow 18\%$; f , $\downarrow 19\%$) in HD animals were not considered drug related due the lack of dose-relationship and the findings in untreated animal (σ , $\downarrow 18\%$, f , $\downarrow 1\%$).

Toxicokinetics:

Lower limit of quantification (LLOQ) was $0.25 \mu\text{g/L}$ for B9207-021 using 0.05 ml mouse serum. Due to low serum concentrations and to limited available time points, evaluation of the drug concentrations was focused on that at 1 hour post-dose. As presented in the table below, there was no dose accumulation occurred during the 2-year treatment period.

Mean serum concentrations of B9207-021 at 1 hour post-dose (mcg/L)

Dose (mcg/kg)	Day 1	Day 176	Day 358	Day 729
150	All values <LLOQ			n.a.
450	0.235	LLOQ	0.120	0.024
900	0.515	0.099	0.259	0.221

Gross pathology:

Increased incidences of lung congestion at MD and HD were observed. Hair loss at HD was also reported although no similar findings were reported in clinical signs.

Histopathology:

Non-neoplastic findings:

Increased incidences of hyperplastic changes in the epithelium of the stomach antrum and more particularly at the junction of the antrum and the duodenum, were noted at MD and HD, mainly in males. A marginally increased incidence and degree of focal squamous metaplasia at the junction of the antrum and the duodenum was also seen in MD and HD groups, mainly in females. The incidences of osteosclerosis of femur and/or tibia, and sternum were increased in females at MD and HD but no similar changes were seen in males. Slight increased incidences of lung congestion were observed at MD and HD.

Increased incidences of epithelial thinning/basophilia in the esophagus seen in MD and HD females were not considered toxicological significant as it was focal, generally graded as minimal.

The table below presents the incidence of non-neoplastic findings in this study.

The incidences of non-neoplastic changes in the 2-year mouse study

mcg/kg	0	0 (v)	150	450	900	0	0 (v)	150	450	900
	male					female				
n	50	50	50	50	50	50	50	50	50	50
Stomach										
Epi.hyperplasia-antrum and/or junction of antrum and duodenum	7(1.6)	2(1)	9(1.6)	23(2.1)	17(2.1)	5(1.2)	4(1.3)	4(2)	3(1)	5(1.6)
Polypoid at junction of antrum and duodenum	0	0	1(4)	0	0	0	0	0	0	1(2)
Glandular tissue/cystic glandular tissue in submucosa	2	0	2	2	4	1	1	1	0	4
Cystic glandular tissue in tunica muscularis-antrum	0	0	0	0	0	0	0	0	0	1
Focal squamous metaplasia at junction of antrum and duodenum	3(1)	0	3(1.3)	3(1.7)	4(1.3)	1(1)	1(1)	1(2)	6(1.5)	4(1.5)
Esophagus										
Epithelial thinning/basophilia	1(1)	3(1.3)	3(1)	11(1)	4(1)	11(1)	10(1)	15(1)	24(1)	19(1)
Bone										
Osteosclerosis-femur/tibia	2(2)	1(2)	4(2)	2(2)	3(2)	3(2.4)	36(2.6)	39(2.6)	48(2.6)	47(2.9)
Osteosclerosis-sternum	0	0	0	0	0	44(2.8)	46(2.7)	46(2.9)	48(3.1)	48(3.3)
Lung congestion	1	5	2	6	7	3	5	6	7	10

The numbers in parenthesis indicate the severity grade as minimal=1, slight=2, moderate=3 and marked=4

The findings of stomach epithelial hyperplasia and squamous metaplasia seemed correlated with the findings of stomach adenoma. However, the trends of these precursor findings in each gender were not consistent with that of stomach adenoma. Dose relationship for the hyperplasia and metaplasia were not clear. Again, stomach adenoma was not considered a significant finding.

Neoplastic findings:

The sponsor's summary for group distribution of neoplastic findings is presented in appendix, pages 23-28)

The only drug related finding was Adenoma of the antrum of stomach, an unusual tumor in mice, in both sexes at high dose and a male at mid dose. The tumors were small, focal solitary, did not affect survival rate. Historic data indicate that

gastric adenoma in B6C3F1 mice was a spontaneous finding at a low frequency (0-2.1%).

The table below presents the tumor incidence in stomach.

group	Male					Female				
	0	0 (v)	150	450	900	0	0 (v)	150	450	900
mcg/kg	0	0 (v)	150	450	900	0	0 (v)	150	450	900
Total organ examined	50	50	50	50	50	50	50	50	50	50
stomach										
adenoma	0	0	0	1	1	0	0	0	0	3
adenocarcinoma	0	0	0	0	0	0	0	0	0	0

Statistical Analysis by the Biometric group regarding the stomach adenoma revealed positive in trend test in females (Exact method, P=0.0168; Asymptotic method, P=0.0046) compared with the vehicle control. However, pair wise test by Fisher's Exact method revealed no significant difference between the HD females and vehicle control (p>0.05). Due to a lack of statistical significance in pair-wise test between HD and vehicle group, the finding of stomach adenoma was not considered biologically significant.

There were no additional positive findings when tumors were combined according to the Guidelines by McConnell et al (JNCI 74:283-289) and analyzed using trend analysis and the Fishers Exact test.

Conclusions:

The study was adequately performed. An MTD was reached based on the decreased body weight at HD (↓ 9-15% of untreated and 6-7% of vehicle) and corticosteroid effects. Food consumptions were not affected by the drug.

Mice given ciclesonide orally were observed with slight steroid effects (decrease of body weights and increased incidence and/or degree of osteosclerosis in drug treated animals), but not significant increases of tumor incidences.

Carcinogenicity Inhalation Study of B9207-015 in Metered Dose Inhaler (MDI) in Wistar (WU) Rats.

Toxicokinetics of Ciclesonide in an Inhalative Carcinogenicity Study in Wistar Rats (aerosol generated from metered dose inhalers)

Study report #: Main study 176/99 and TK study 177/99 (Byk Gulden's #).

Volume #: Main study 50.1- 50.4, TK study 50.5.

Conducting Lab. and location: The main study: _____
_____ : Byk Gulden Pharmaceuticals, Dept. of
Pharmacokinetics and Drug Metabolism, Germany.
Research, _____

b(4)

Study period: 04/30/1997 – 06/27/2001.

GLP compliance: Yes.

Quality assurance: Yes.

Drug lot #, and purity: Batch CT970137 was used until 03/10/1998, batch 97J01 was used afterward

CAC concurrence: No recommended doses provided due to insufficient data (Mark Vogel, July 14, 1998).

Study type: 2 year bioassay

b(4)

Species/strain: Wistar-derived Rat strain ← WI(WU) BR.

Number/sex/group; age at start of study: (54 ♂ +56 ♀)/dose; 7 weeks old

Animal housing: 2 (same sex)/cage.

b(4)

Formulation/vehicle: —, ethanol, —, ciclesonide. Propellant was not indicated in the analytic report.

Drug stability/homogeneity: Not provided.

Methods:

Doses: 1.0, 2.5, and 6.25 mg/m³ drug aerosol for 1 hour

Basis for dose selection: MTD

Restriction paradigm for dietary restriction studies: N/A

Route of drug administration: Inhalation

Frequency of drug administration: 1 hour/day for 2 years.

Dual controls employed: Clean air and vehicle

Interim sacrifice: No

Satellite PK or special study groups: 6/sex per drug dosed group.

Deviation from original study protocol: Nothing significant

Observations and times:

Clinical signs: Daily

Body weights: Weekly in the first 13 weeks and monthly thereafter.

Food consumption: Weekly during the first 13 weeks and monthly thereafter.

Hematology: At termination, surviving animals.

Clinical chemistry: Not performed.

Toxicokinetics: The blood samples were collected once before dosing, and 1, 2, 4 and 22 hours after dosing during the second exposure week, after one year of exposure and during the last exposure week.

Ethanol in plasma: On day 100, 5/sex of air control and vehicle control.

Gross pathology: At necropsy.

Organ weights: Not measured.

Histopathology: At termination, a complete battery of tissues was examined in all groups (histopathology inventory, pages 20-21).

Results:

Delivered doses:

Group	Aerosol conc. (µg/L)	Dose duration/day (min)	Delivered dose (ug/kg)	
			♂	♀
LD	1.01	60	28	32
MD	2.5	60	70	81
HD	6.26	60	179	207

Mortality: No drug-related mortality was observed. Details are presented in the following tables and figures.

Table 6: Cumulative Mortality Males

Carcinogenicity Inhalation Study of B9207-015 in Metered Dose Inhaler (MDI) in Wistar (WU) Rats
Study : 02G97006 . Toxikologie u. Aerosolforsch.

b(4)

Cumulative mortality

Cumulative number of animals found dead or killed in extremis.

M A L E S		Control		1 mg/m ³		2.5 mg/m ³		6.25 mg/m ³		Vehicle	
DAY	n	n	%	n	%	n	%	n	%	n	%
DAY 0	0	0	0%	0	0%	0	0%	0	0%	0	0%
DAY 30	0	0	0%	0	0%	0	0%	0	0%	0	0%
DAY 60	0	0	0%	0	0%	0	0%	0	0%	0	0%
DAY 90	1	1	2%	0	0%	0	0%	0	0%	0	0%
DAY 120	1	1	2%	0	0%	0	0%	0	0%	0	0%
DAY 150	1	1	2%	0	0%	0	0%	0	0%	0	0%
DAY 180	1	1	2%	0	0%	0	0%	0	0%	0	0%
DAY 210	1	1	2%	0	0%	0	0%	0	0%	0	0%
DAY 240	1	1	2%	0	0%	0	0%	0	0%	0	0%
DAY 270	1	1	2%	0	0%	0	0%	0	0%	0	0%
DAY 300	1	1	2%	0	0%	0	0%	0	0%	0	0%
DAY 330	1	1	2%	1	2%	0	0%	0	0%	1	2%
DAY 360	1	1	2%	2	4%	0	0%	0	0%	1	2%
DAY 390	1	1	2%	2	4%	0	0%	0	0%	1	2%
DAY 420	1	1	2%	2	4%	0	0%	0	0%	3	6%
DAY 450	1	1	2%	2	4%	0	0%	0	0%	3	6%
DAY 480	1	1	2%	3	6%	0	0%	1	2%	3	6%
DAY 510	1	1	2%	3	6%	0	0%	1	2%	4	7%
DAY 540	2	2	4%	3	6%	0	0%	3	6%	4	7%
DAY 570	3	3	6%	3	6%	0	0%	3	6%	5	9%
DAY 600	3	3	6%	3	6%	1	2%	4	7%	5	9%
DAY 630	4	4	7%	4	7%	1	2%	4	7%	7	13%
DAY 660	4	4	7%	4	7%	2	4%	4	7%	7	13%
DAY 690	5	5	9%	5	9%	2	4%	6	11%	10	19%
DAY 720	8	8	15%	5	9%	5	9%	7	13%	12	22%
DAY 750	8	8	15%	7	13%	8	15%	8	15%	13	24%

Including all animals till last day of final sacrifice (day 750)

Table 7: Cumulative Mortality Females

b(4)

Carcinogenicity Inhalation Study of B9207-015 in Metered Dose Inhaler (MDI) in Wistar (WU) Rats
Toxicologie u. Aerosolforsch.
Study : 02G97006

Cumulative mortality

Cumulative number of animals found dead or killed in extremis.

F E M A L E S

	Control		1 mg/m ³		2.5 mg/m ³		6.25 mg/m ³		Vehicle	
	n	%	n	%	n	%	n	%	n	%
DAY 0	0	0%	0	0%	0	0%	0	0%	0	0%
DAY 30	0	0%	0	0%	0	0%	0	0%	0	0%
DAY 60	0	0%	0	0%	0	0%	0	0%	0	0%
DAY 90	0	0%	0	0%	0	0%	0	0%	0	0%
DAY 120	0	0%	0	0%	0	0%	0	0%	0	0%
DAY 150	0	0%	0	0%	0	0%	0	0%	0	0%
DAY 180	0	0%	0	0%	0	0%	0	0%	1	2%
DAY 210	0	0%	0	0%	0	0%	0	0%	1	2%
DAY 240	0	0%	0	0%	0	0%	0	0%	1	2%
DAY 270	1	2%	0	0%	0	0%	0	0%	1	2%
DAY 300	1	2%	0	0%	0	0%	0	0%	1	2%
DAY 330	1	2%	0	0%	0	0%	1	2%	1	2%
DAY 360	1	2%	0	0%	0	0%	1	2%	2	4%
DAY 390	2	4%	0	0%	1	2%	1	2%	2	4%
DAY 420	2	4%	1	2%	2	4%	2	4%	7	13%
DAY 450	2	4%	2	4%	4	7%	2	4%	7	13%
DAY 480	2	4%	2	4%	5	9%	2	4%	7	13%
DAY 510	5	9%	4	7%	5	9%	3	5%	7	13%
DAY 540	6	11%	5	9%	6	11%	4	7%	9	16%
DAY 570	7	13%	5	9%	6	11%	4	7%	9	16%
DAY 600	8	14%	7	13%	7	13%	5	9%	10	18%
DAY 630	12	21%	9	16%	8	14%	6	11%	10	18%
DAY 660	12	21%	13	23%	11	20%	7	13%	11	20%
DAY 690	14	25%	15	27%	13	23%	9	16%	13	23%
DAY 720	16	29%	17	30%	15	27%	10	18%	16	29%
DAY 750	16	29%	17	30%	16	29%	12	21%	17	30%

Including all animals till last day of final sacrifice (day 750)

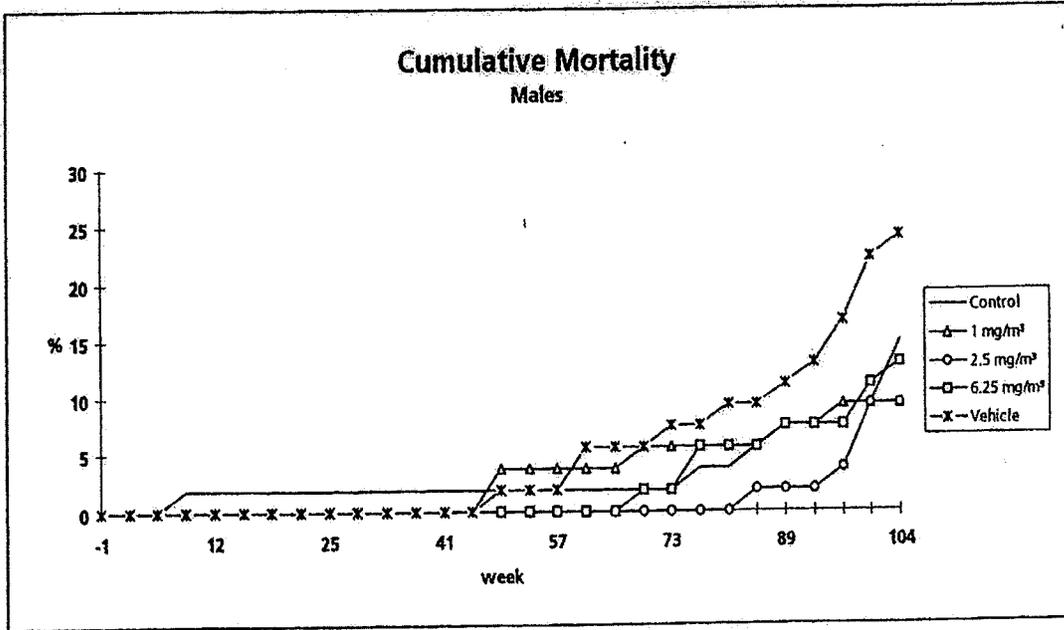


Figure 4: Cumulative Mortality Males

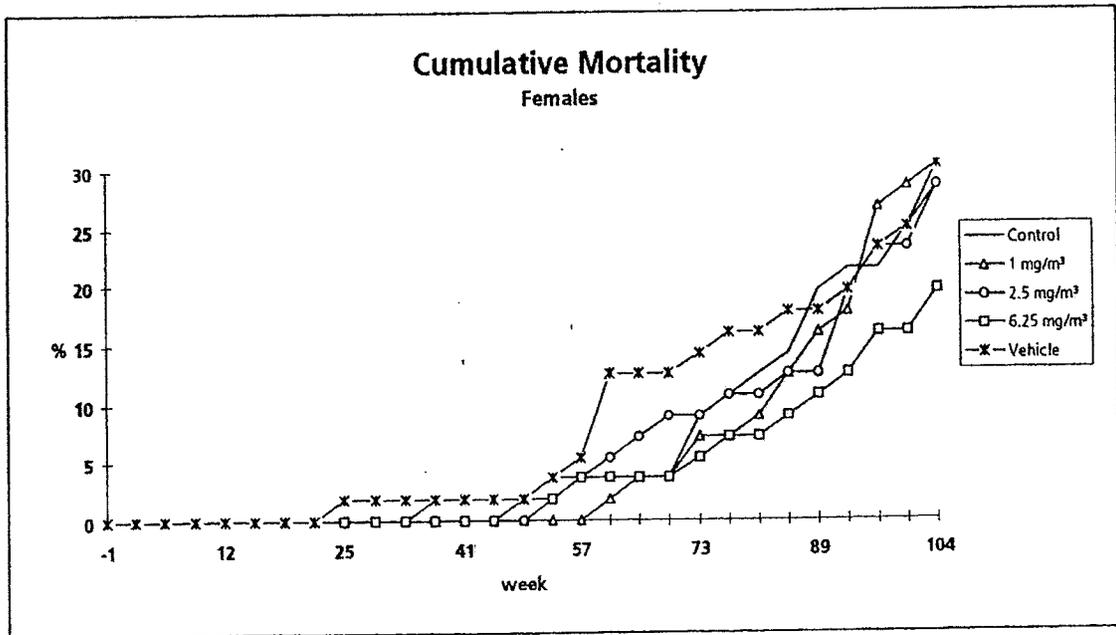


Figure 5: Cumulative Mortality Females

Clinical observations:

Drug-related alopecia, especially in the neck/back region was noted in male at HD and females at all doses from Week 18 through the end of the study.

Sialodacryoadenitis and nodule/mass of mammary glands were seen in both controls and drug treated groups, and were not considered drug-related. The incidences of above findings at week 104 are presented in the following table.

Group	Alopecia (%)		Sialodacryoadenitis (%)		Mammary gland mass (%)	
	♂	♀	♂	♀	♂	♀
Air	4	15	17	53	2	30
LD	8	33	8	31	4	44
MD	6	39	6	46	0	22
HD	60	83	6	46	2	13
Vehicle	0	13	22	35	2	20

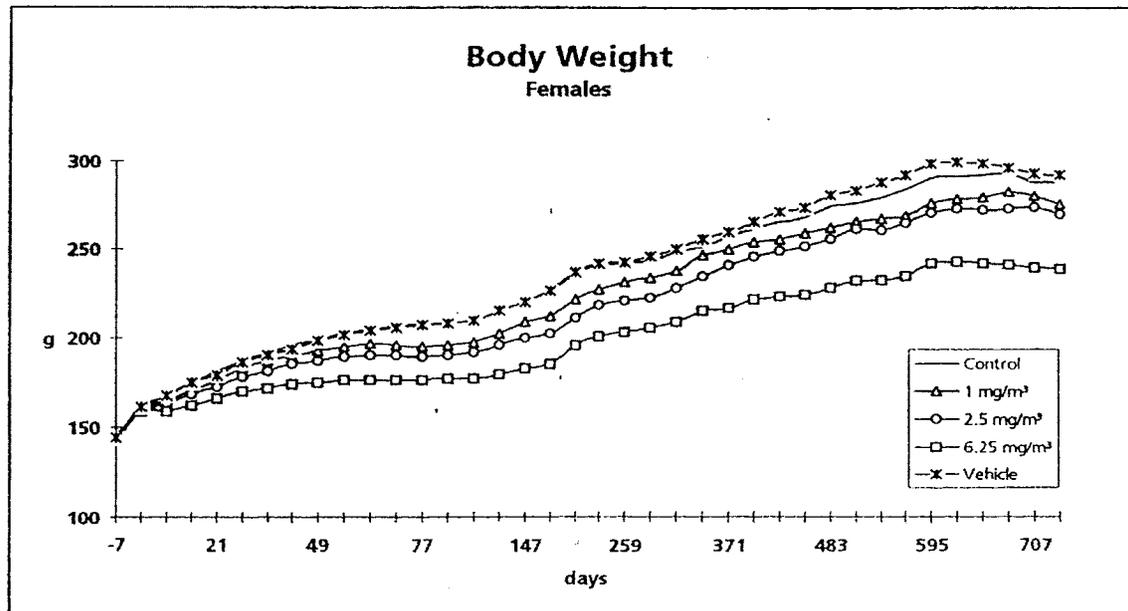
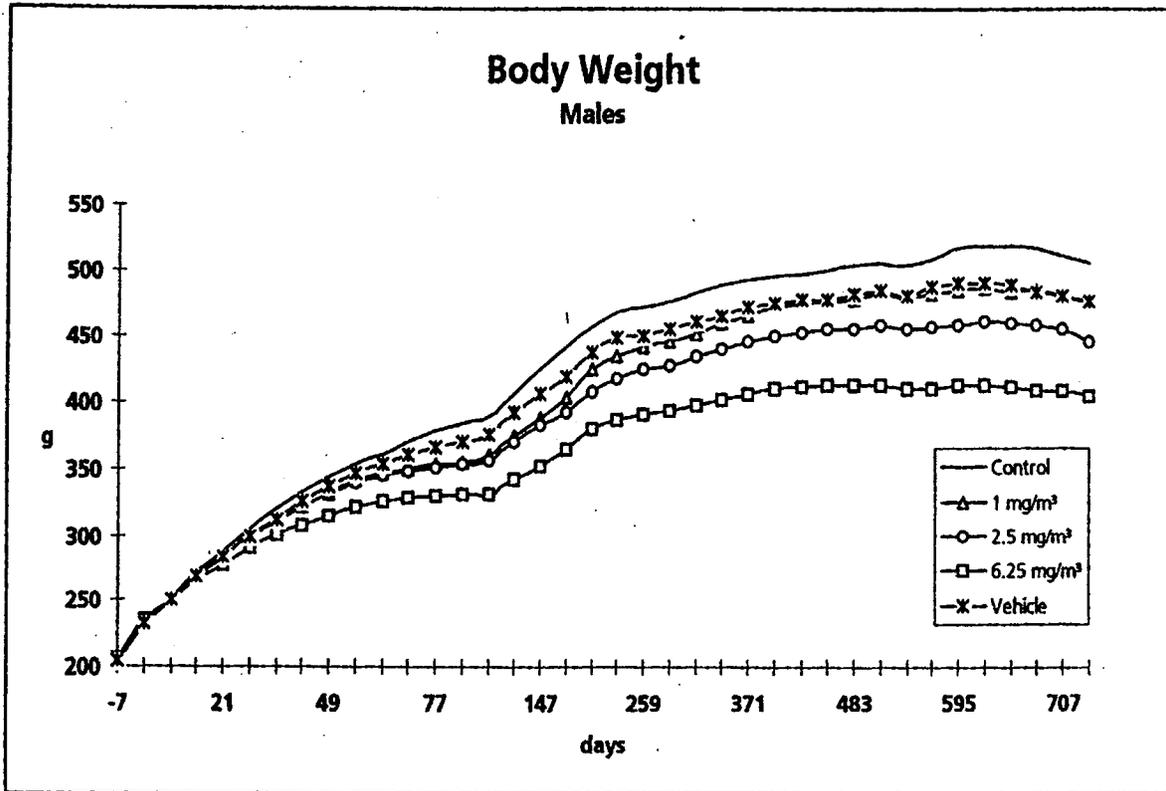
Body weights:

Dose and treatment duration-dependent decreases of body weight were seen in both sexes (detailed in the table below and figures following).

Body weights in the rat 2-yr study

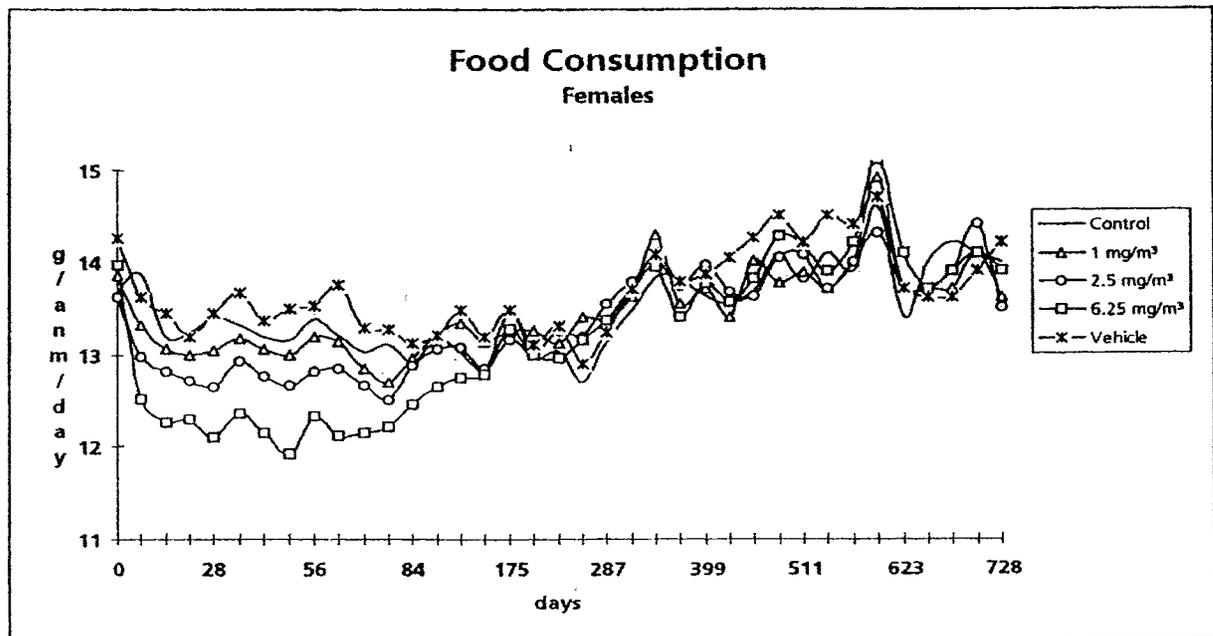
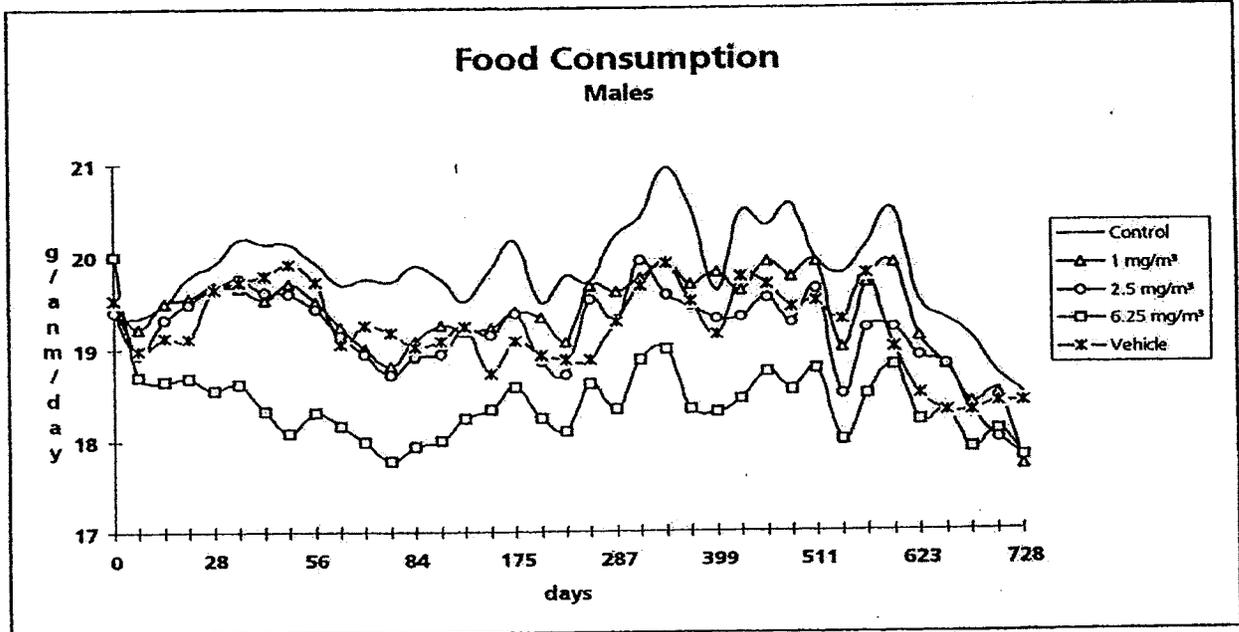
	Male					Female				
	Air	Veh.	LD	MD	HD	Air	Veh.	LD	MD	HD
Abs wt (g)	506	477	475	447	406	288	292	275	270	239
% of air	-	94	94	88	80	-	101	95	94	83
% of veh.	106	-	100	94	85	99	-	94	92	82

veh.=vehicle



Food consumption:

Males had decreased food consumptions of 3, 5, 8, 5% at LD, MD, HD and vehicle, respectively. Females showed only at the first 3.5 months lower food consumption (MD, 6%; HD, 7%) compared to the air control group.



Hematology:

Dose-related decreases were observed in total white blood cell count (HD ♂, 19%; HD ♀, 21%), and absolute lymphocyte count (♂: MD, 16%; HD, 26%; ♀: LD, 12.9%; MD, 8.7%; HD, 25.3%).

Toxicokinetics:

Due to low serum concentrations of B9207-021 and limited time points, only limited pharmacokinetics were obtained. Estimation of the AUCs up to 6 hours were performed for the high dose group only. These partial AUCs were slightly underestimated resulting in geometric means of 3.0, 6.6 and 4.9 µg.h/ml for day 1, 366 and 724, respectively. Based on the serum concentrations of B9207-021 at 1 h after the drug administration on day 1, 366 and 724, it was concluded that drug exposure was proportional to the doses and no drug accumulation occurred over the 2-year dosing period, there was no gender difference in the pharmacokinetics.

Ethanol in plasma:

Ethanol levels were determined in air and vehicle control groups on Day 100 (LLOQ = 0.05 mmol/l) and there were no detectable levels of ethanol in plasma from either one of these groups.

Gross pathology:

Drug-related alopecia was noted (as described in clinical signs).

Histopathology:

Non-neoplastic

The findings included increased incidences of lung alveolar histiocytosis and cholesterol clefts or granuloma(ta), hepatocellular fatty vacuolation, islet-cell hyperplasia, adrenal cortical hyperplasia, ovarian cysts, and thymic atrophy. Corresponding to the finding of "alopecia", slight to severe atrophy of the hair follicles were observed. Additionally, focal epidermal hyperplasia, hyperkeratosis, and inflammatory cell infiltrations were observed in the skin and considered related to drug induced reduction of local resistance.

The table below summarizes the incidences of non-neoplastic findings in this study.

Incidence of non-neoplastic findings

findings	male				female			
	Air/veh.	LD	MD	HD	Air/veh.	LD	MD	HD
# of animals observed	54/54	54	54	54	56/56	56	56	56
Alveolar histiocytosis	18/18	15	19	27	13/19	15	19	20
Lung cholesterol cleft/granuloma	2/2	1	5	7	1/0	0	0	4
Liver fatty vacuolation	4/9	4	4	13	3/4	3	2	12
Islet cell hyperplasia	0/2	1	4	8	0/0	0	1	1
Adrenal cortical hyperplasia	1/1	1	3	4	1/1	1	1	4
Ovary cyst					12/13	14	15	20
Skin hair follicle atrophy	2/0	2	3	30	8/5	12	21	42
Skin epidermal hyperplasia	0/1	1	0	0	0/0	2	4	1
hyperkeratosis	0/0	2	0	1	0/1	1	2	2
Thymic atrophy	42/46	38	40	41	29/33	23	32	41

Neoplasms: (sponsor's summary tables for tumor incidences are presented in the appendix, pages 29-34)

There were no drug-related increases of benign or malignant tumors in this study. Statistical analysis by the Biometric group revealed no positive trends in any single tumor or combined tumors (according to the Guidelines by McConnell et al, JNCI 74:283-289), in male or female rats.

Conclusion:

The study was adequately performed. The MTD was reached based on the decreases of body weights at HD (↓ 17-20% of air control and ↓ 15-18% of vehicle control). The body weight decrease was accompanied by slight lower food consumption (≤8%).

Ciclesonide caused typical glucocorticoid effects including decreases of body weights and food consumptions, decreases of white blood cell counts primarily lymphocyte counts, increased incidences of lung alveolar histiocytosis, hepatocellular fatty vacuolation, adrenal cortical hyperplasia, ovarian cysts, and skin hair follicle atrophy.

The test compound did not cause increases of tumors.

Histopathology Inventory for IND # 53391

Study	2y car	2y car		
Species	rat	mice		
Adrenals	X	X		
Aorta	X	X		
Bone Marrow smear	X	X		
Bone (femur)	X	X		
Brain	X	X		
Cecum	X	X		
Cervix				
Colon	X	X		
Duodenum	X	X		
Epididymis	X	X		
Esophagus		X		
Eye	X	X		
Middle/inner ear				
Fallopian tube				
Gall bladder		X		
Gross lesions		X		
Harderian gland		X		
Heart	X	X		
Ileum	X	X		
Injection site				
Jejunum		X		
Kidneys	X	X		
Lachrymal gland		X		
Larynx	X			
Liver	X	X		
Lungs	X	X		
Lymph nodes, cervical				
Lymph nodes, tracheobronchial				
Lymph nodes mandibular		X		
Lymph nodes, mesenteric	X	X		
Mammary Gland	X	X		
Nasal cavity	X			
Optic nerves		X		
Ovaries	X	X		
Pancreas	X	X		
Parathyroid				
Peripheral nerve				
Pharynx				
Pituitary	X	X		
Prostate	X	X		
Rectum	X	X		
Salivary gland	X	X		
Sciatic nerve	X			

Seminal vesicles		X		
Skeletal muscle	X			
Skin				
Spinal cord	X	X		
Spleen	X	X		
Sternum		X		
Stomach	X	X		
Testes	X	X		
Thymus	X	X		
Thyroid	X	X		
Tongue	X	X		
Trachea	X			
Tracheal bifurcation				
Urinary bladder	X	X		
Uterus	X	X		
Vagina	X			
Zymbal gland	X	X		
Standard List				

X, histopathology performed
*, organ weight obtained

Summary of Carcinogenicity

2-year carcinogenicity studies were conducted in rats by inhalation and mice by oral gavage.

Mice receiving ciclesonide at oral doses of 150, 450 and 900 mcg/kg were observed with slight glucocorticoid effects (decreases of body weights and increases of incidences of osteosclerosis). The study is acceptable. Gastric adenoma was observed at MD and HD. The incidence was statistically significant by trend test but not pair-wise fisher's exact test for any dose levels. Therefore, the finding of gastric adenoma was not considered biologically significant.

Rats receiving ciclesonide by inhalation at delivered doses of 30, 76, and 193 mcg/kg resulted in dose-related changes including decreases of body weights, food consumption, and white blood cell counts, and increases of lung alveolar histiocytosis, hepatocyte fatty vacuolation, and adrenal cortical hyperplasia. The study is acceptable. Tumor incidences were not increased by ciclesonide in this study.

In conclusion, this drug is not tumorigenic in rats and mice.

Recommendation:

Negative findings in 2-year mouse and rat studies were concluded pending on concurrence from the Executive CAC (June 8, 2004).

Huiqing Hao, Ph.D., Pharmacologist

Appendix:

Neoplastic findings in mice (pages 23-28)

TABLE 9

Histopathology - group distribution of neoplastic findings for all animals

b(4)

Print No: 0028
Printed: 15-APR-02
protocol Number: BYG 059

NEOPLASM CLASSIFICATION SUMMARY	--- NUMBER OF ANIMALS AFFECTED ---									
	SEX: MALE					SEX: FEMALE				
	GROUP: -1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NEOPLASM CLASSIFICATION SUMMARY	NUMBER: 50	50	50	50	50	50	50	50	50	50
TOTAL PRIMARY NEOPLASMS	52	35	37	40	35	53	54	48	51	46
ANIMALS WITH ONE OR MORE	38	31	28	24	25	35	36	33	33	31
PERCENT WITH ONE OR MORE	76%	62%	56%	48%	50%	70%	72%	66%	66%	62%
TOTAL BENIGN NEOPLASMS	37	25	25	35	25	27	28	20	28	25
ANIMALS WITH ONE OR MORE	29	22	22	23	20	19	22	16	18	20
PERCENT WITH ONE OR MORE	58%	44%	44%	46%	40%	38%	44%	32%	36%	40%
TOTAL MALIGNANT NEOPLASMS	15	10	11	5	10	26	26	28	23	21
ANIMALS WITH ONE OR MORE	14	10	11	4	8	26	24	24	22	17
PERCENT WITH ONE OR MORE	28%	20%	22%	8%	16%	52%	48%	48%	44%	34%
+ TOTAL METASTATIC NEOPLASMS	80	59	61	22	35	220	203	202	145	67
ANIMALS WITH ONE OR MORE	10	7	9	3	4	23	21	22	20	13
PERCENT WITH ONE OR MORE	20%	14%	18%	6%	8%	46%	42%	44%	40%	26%

+ This includes multiple sites of multicentric tumours, such as lymphoma

(Histopathology - group distribution of neoplastic findings for animals killed or dying during the study - continued)

Print No: 0019

Group : 1 2 3 4 5
Compound : Control PEG 400 -89207-015 (Ciclesonide)
Dosage (ug/kg/day) 0 0 150 450 900

Printed: 31-MAR-01

protocol number: BYG 059

b(4)

--- NUMBER - OF - ANIMALS - AFFECTED ---

ORGAN AND FINDING DESCRIPTION	NUMBER	SEX: MALE					SEX: FEMALE				
		GROUP: -1- -2- -3- -4- -5-					GROUP: -1- -2- -3- -4- -5-				
		-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
BONE	NUMBER EXAMINED:	0	1	0	0	0	1	0	0	0	1
--M-OSTEOSARCOMA		0	0	0	0	0	0	0	0	0	1
H*POIETIC TUMOUR	NUMBER EXAMINED:	8	7	8	3	9	11	10	9	8	6
--M-PLEOMORPHIC LYMPHOMA		3	1	1	0	2	1	0	1	4	1
--M-LYMPHOBLASTIC/LYMPHOCYTIC LYMPHOMA		0	0	2	0	0	4	3	2	0	0
--M-MALIGNANT LYMPHOMA (UNCLASSIFIED)		0	0	0	0	0	1	0	0	1	1
--M-HISTIOCYTIC SARCOMA		0	0	0	0	0	0	0	2	0	0
MEDIASTINUM	NUMBER EXAMINED:	0	0	0	0	1	2	1	0	1	0
--M-HAEMANGIOSARCOMA		0	0	0	0	0	0	0	0	1	0
UTERUS	NUMBER EXAMINED:	0	0	0	0	0	11	9	9	8	6
--M-HAEMANGIOSARCOMA		0	0	0	0	0	0	0	1	0	0

** END OF LIST **

Histopathology - group distribution of neoplastic findings for animals killed after 104 weeks of treatment

Print No: 0020

Printed: 31-MAR-01

Group : 1 2 3 4 5
Compound : Control PEG 400 -B9207-015 (Ciclesonide)
Dosage (ug/kg/day) 0 0 150 450 900

protocol number: BYG 059

b(4)

--- NUMBER OF ANIMALS AFFECTED ---											
ORGAN AND FINDING DESCRIPTION	NUMBER	SEX: MALE					SEX: FEMALE				
		GROUP: -1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
** TOP OF LIST **											
ADRENALS	NUMBER EXAMINED:	42	43	42	47	41	39	40	41	42	44
--B-CORTICAL ADENOMA		0	1	1	1	2	0	0	0	0	0
--B-CORTICAL ADENOMA, FUSIFORM		0	0	0	1	1	0	0	0	0	0
--B-CORTICAL ADENOMA, POLYGONAL		1	2	0	4	2	0	1	0	0	0
--B-PHAECHROMOCYTOMA		0	0	0	0	0	1	0	1	0	0
COLON	NUMBER EXAMINED:	42	43	42	47	41	39	40	41	42	44
--B-LEIOMYOMA		0	0	0	0	0	0	0	0	1	0
DUODENUM	NUMBER EXAMINED:	42	43	42	47	41	39	40	41	42	44
--M-EARLY ADENOCARCINOMA		0	0	0	0	0	0	0	0	0	1
HARDERIAN GLANDS	NUMBER EXAMINED:	42	43	42	47	41	39	40	41	42	44
--B-ADENOMA		6	1	4	5	1	2	3	2	3	3
--M-ADENOCARCINOMA		0	0	1	1	0	0	0	0	0	0
KIDNEYS	NUMBER EXAMINED:	42	43	42	47	41	39	40	41	42	44
--B-TUBULAR ADENOMA		0	1	0	0	1	0	0	0	0	0
L N MESENTERIC	NUMBER EXAMINED:	42	43	42	46	41	39	40	41	42	43
--B-HAEMANGIOMA		0	0	0	1	0	0	0	0	0	0
LIVER	NUMBER EXAMINED:	42	43	42	47	41	39	40	41	42	44
--B-HEPATOCELLULAR ADENOMA		13	13	11	10	7	2	2	1	5	2
--M-HEPATOCELLULAR CARCINOMA		4	2	2	1	1	0	0	3	1	1
--B-HAEMANGIOMA		2	0	0	0	0	0	0	0	0	0
LUNGS/BRONCHI	NUMBER EXAMINED:	42	43	42	47	41	39	40	41	42	44
--B-BRONCHIOLOALVEOLAR ADENOMA		4	4	5	9	7	3	6	1	0	4
--M-BRONCHIOLOALVEOLAR ADENOCARCINOMA		1	1	0	0	1	0	0	1	1	1

(Histopathology - group distribution of neoplastic findings for animals killed after 104 weeks of treatment - continued)

Print No: 0020

Printed: 31-MAR-01

Group : 1 2 3 4 5
Compound : Control PEG 400 -B9207-01S (Ciclesonide)
Dosage (ug/kg/day) 0 0 150 450 900

protocol number: BYG 059

b(4)

ORGAN AND FINDING DESCRIPTION	--- NUMBER OF ANIMALS AFFECTED ---										
	SEX: MALE					SEX: FEMALE					
	GROUP: -1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-	
	NUMBER:	42	43	42	47	41	39	40	41	42	44
PANCREAS	NUMBER EXAMINED:	42	43	42	47	41	39	40	41	42	44
--B-ISLET CELL ADENOMA		1	0	1	1	0	0	2	1	2	1
PITUITARY	NUMBER EXAMINED:	42	43	42	47	41	39	40	41	42	43
--B-ADENOMA - PARS DISTALIS		0	0	0	0	0	10	4	6	6	5
--M-CARCINOMA - PARS DISTALIS		0	0	0	0	0	0	0	0	0	1
--B-ADENOMA - PARS INTERMEDIA		0	0	0	0	0	0	1	1	0	0
SPLEEN	NUMBER EXAMINED:	42	43	42	47	41	39	40	41	42	44
--B-HEMANGIOMA		1	0	0	1	0	0	0	0	0	0
STOMACH	NUMBER EXAMINED:	42	43	42	47	41	39	40	41	42	44
--B-SQUAMOUS CELL PAPILLOMA		0	0	0	0	0	1	0	0	0	1
--B-ADENOMA (ANTRUM)		0	0	0	1	0	0	0	0	0	3
TESTES	NUMBER EXAMINED:	42	43	42	47	41	0	0	0	0	0
--B-INTERSTITIAL (LEYDIG) CELL ADENOMA		2	0	1	0	1	0	0	0	0	0
THYMUS	NUMBER EXAMINED:	39	41	41	43	38	39	40	40	41	41
--B-THYMOMA (LYMPHOID)		0	0	0	0	0	0	1	0	0	0
THYROIDS	NUMBER EXAMINED:	42	43	42	47	41	39	40	41	42	44
--B-FOLLICULAR CELL ADENOMA		0	0	0	0	0	0	1	0	1	0
UTERINE CERVIX	NUMBER EXAMINED:	0	0	0	0	0	39	40	41	42	44
--B-GRANULAR CELL TUMOUR		0	0	0	0	0	0	0	0	1	0
--M-FIBROSARCOMA		0	0	0	0	0	1	0	0	0	0
VAGINA	NUMBER EXAMINED:	0	0	0	0	0	39	40	41	42	44
--M-SQUAMOUS CELL CARCINOMA		0	0	0	0	0	0	1	0	0	0

Neoplastic findings in Rats (pages 29 to 34)

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Carcinogenicity Inhalation Study of B9207-015 in Metered Dose Inhaler (MDI) in Wistar (WU) Rats

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Table 21: Tumor Table

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Tumor Table

LESIONS	TREATMENT	TUMOR TABLE											
		Males						Females					
		IClean	11	12.5	16.25	IVehi-	IClean	11	12.5	16.25	IVehi-		
IAir	1mg/m3	1mg/m3	1mg/m3	ICle	IAir	1mg/m3	1mg/m3	1mg/m3	ICle				
IContr.	189207-	189207-	189207-	IContr.	IContr.	189207-	189207-	189207-	IContr.				
		1015	1015	1015		1015	1015	1015					
NUMBER OF ANIMALS		54	54	54	54	56	56	56	56	56	56		
NUMBER OF ANIMALS WITH TUMORS		39	33	37	34	28	43	46	41	37	39		
NUMBER OF ANIMALS WITH SINGLE TUMORS		25	25	22	25	19	24	24	25	23	22		
NUMBER OF ANIMALS WITH MULTIPLE TUMORS		14	8	15	9	9	19	22	16	14	17		
NUMBER OF ANIMALS WITH BENIGN TUMORS		35	30	35	30	24	42	45	40	36	36		
NUMBER OF ANIMALS WITH MALIGNANT TUMORS		9	5	7	6	6	5	7	3	6	6		
NUMBER OF ANIMALS WITH METASTASISING TUMORS		1			1	1	1				1		
TOTAL NUMBER OF TUMORS		61	42	57	44	37	70	75	60	53	65		
TOTAL NUMBER BENIGN TUMORS		52	37	50	38	31	64	68	57	47	59		
TOTAL NUMBER OF MALIGNANT TUMORS		9	5	7	6	6	6	7	3	6	6		
TOTAL NUMBER OF METASTASISING TUMORS		1			1	1	1				1		
% ANIMALS WITH TUMORS		72	61	69	63	52	77	82	73	66	70		
% ANIMALS WITH SINGLE TUMORS		46	46	41	46	35	43	43	45	41	39		
% ANIMALS WITH MULTIPLE TUMORS		26	15	28	17	17	34	39	29	25	30		
% ANIMALS WITH BENIGN TUMORS		65	56	65	56	44	75	80	71	64	64		
% ANIMALS WITH MALIGNANT TUMORS		17	9	13	11	11	9	13	5	11	11		
% ANIMALS WITH METASTASISING TUMORS		2			2	2	2				2		

*** Listing Complete ***

Study : 02G97006* APPROVED PROTOCOL *

Table 22: Summary of Tumor Incidence

b(4)

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Page: 1

Summary of Tumor Incidence

LESIONS	TREATMENT	INCIDENCE OF TUMORS (NUMERIC)									
		Males					Females				
		Clean	12.5	16.25	1Veh1-	Clean	12.5	16.25	1Veh1-		
		1Atr	1mg/m3	1mg/m3	1mg/m3	1cle	1Atr	1mg/m3	1mg/m3	1mg/m3	1cle
		1Contr.189207-189207-189207-1									
		1015	1015	1015	1	1015	1015	1015	1	1	
CEREBRUM		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(56)
OLIGODENDROGLIOMA [M]		0	0	0	0	0	0	0	0	1	0
Mixed GLIOMA [B]		1	0	0	0	0	0	0	0	0	0
GRANULAR CELL TUMOR [B]		1	0	0	0	1	0	0	0	0	0
CEREBELLUM		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(56)
Mixed GLIOMA [B]		0	0	0	1	0	0	0	0	0	0
GRANULAR CELL TUMOR [B]		0	0	0	1	1	0	0	0	0	0
PITUITARY		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(55)
Pars distalis ADENOCARCINOMA [M]		0	0	0	0	1	0	0	1	0	0
Pars distalis ADENOMA(TA) [B]		13	9	18	9	9	27	27	18	14*	21
LUNGS		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(56)
BRONCHIOLO-ALVEOLAR CARCINOMA [M]		1	0	0	0	1	0	0	0	0	0
THYROID		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(56)
C-CELL CARCINOMA [M]		0	0	0	0	0	1	0	0	0	0
C-CELL ADENOMA(TA) [B]		7	3	4	5	1	3	1	1	0	4
FOLLICULAR CELL ADENOMA [B]		1	1	1	2	0	0	0	1	0	0
PARATHYROIDS		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(56)
ADENOMA(TA) [B]		3	1	1	0	1	0	1	0	0	1
HEART		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(56)
ATRIOCAVAL MESOTHELIOMA [M]		0	1	0	0	0	0	0	0	0	0
Endocardial SCHWANNOMA [M]		0	0	0	1	1	0	0	0	0	0
Endocardial SCHWANNOMA [B]		1	1	0	0	0	0	0	0	0	0
Intramural SCHWANNOMA [B]		0	0	0	0	0	1	0	0	0	0

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05, **P<0.01, ***P<0.001

[B] Benign tumor

[M] Malignant tumor

Figures in brackets represent the number of animals from which this tissue was examined microscopically

The absence of a numeral indicates that the lesion specified was not identified

Table 22: Summary of Tumor Incidence

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Summary of Tumor Incidence

LESIONS	TREATMENT	INCIDENCE OF TUMORS (NUMERIC)									
		Males					Females				
		Clean Air Contr.	1 189207- 1015	12.5 img/m3 1015	16.25 img/m3 1015	Vehi- icle 1	Clean Air Contr.	1 189207- 1015	12.5 img/m3 1015	16.25 img/m3 1015	Vehi- icle 1
TEETH		(26)	(22)	(21)	(16)	(20)	(9)	(8)	(5)	(7)	(4)
Ameloblastic ODONTOMA [B]		0	0	0	0	0	1	0	0	0	0
SALIVARY GLANDS		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(56)
SCHWANNOMA [M]		0	0	1	0	0	0	0	0	0	0
TONGUE		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(56)
SQUAMOUS-CELL CARCINOMA [M]		1	0	0	0	0	0	0	0	0	0
ABDOMINAL CAVITY		(1)		(2)	(2)		(1)				(2)
MESOTHELIONA [M]		1		0	2		0				0
GLANDULAR STOMACH		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(56)
ADENOCARCINOMA [M]		0	1	0	0	0	0	0	0	0	0
LIVER		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(56)
HEPATOCELLULAR CARCINOMA [M]		2	0	0	0	0	0	0	0	0	0
CHOLANGIOCARCINOMA [M]		1	0	0	0	0	0	0	0	0	0
HEPATOCELLULAR ADENOMA [B]		0	0	1	0	0	0	0	0	0	0
CHOLANGIOMA [B]		0	0	0	0	0	0	0	0	0	1
PANCREAS		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(56)
ACINAR-CELL ADENOCARCINOMA [M]		0	0	0	1	0	0	0	0	0	0
ISLET CELL CARCINOMA [M]		0	0	0	1	0	0	0	0	0	0
ACINAR ISLET-CELL ADENOMA [B]		1	0	0	0	0	0	0	0	0	0
ISLET CELL ADENOMA [B]		0	0	2	0	0	0	0	1	0	0

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05, **P<0.01, ***P<0.001

[B] Benign tumor

[M] Malignant tumor

Figures in brackets represent the number of animals from which this tissue was examined microscopically

The absence of a numeral indicates that the lesion specified was not identified

*** Continued

Table 22: Summary of Tumor Incidence

b(4)

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Summary of Tumor Incidence

LESIONS	TREATMENT	INCIDENCE OF TUMORS (NUMERIC)										
		Males					Females					
		Clean 11 1015	12.5 img/m3 1015	16.25 img/m3 1015	1Vehi- 1cle 1015	Clean 11 1015	12.5 img/m3 1015	16.25 img/m3 1015	1Vehi- 1cle 1015	Clean 11 1015	12.5 img/m3 1015	16.25 img/m3 1015
MESENTERY		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(56)	(56)
SARCOMA, NOS [M]		0	0	1	0	0	0	0	0	0	0	0
LIPOMA [B]		0	0	0	0	1	0	0	0	0	0	0
HAEMANGIOMA [B]		0	1	1	0	0	0	0	0	0	0	0
MESENTERIAL LYMPH NODES		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(56)	(56)
HAEMANGIOSARCOMA [M]		0	0	0	0	0	0	1	0	0	0	0
HAEMANGIOMA(TA) [B]		1	0	1	2	2	2	0	1	0	0	1
RECTUM		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(56)	(56)
GRANULAR CELL TUMOR [B]		0	0	0	0	0	0	0	0	0	0	1
KIDNEYS		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(56)	(56)
RENAL LIPOSARCOMA [M]		0	0	2	0	0	0	0	0	0	0	0
RENAL LIPOMA [B]		0	0	1	0	1	0	0	0	0	0	0
URINARY BLADDER		(53)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(56)	(56)
TRANSITIONAL CELL PAPILLOMA(TA) [B]		0	0	1	0	0	0	0	0	0	1	0
ADRENALS		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(56)	(56)
CORTICAL ADENOCARCINOMA [M]		1	0	0	0	0	0	0	0	0	0	1
PHAECHROMOCYTOMA [M]		0	1	1	0	0	1	0	0	0	0	0
CORTICAL ADENOMA [B]		1	0	2	1	0	1	1	1	1	1	0
PHAECHROMOCYTOMA(TA) [B]		2	1	2	3	2	0	0	0	0	0	1
GANGLIONEUROMA [B]		0	0	0	0	1	0	0	0	0	0	0
TESTES		(54)	(54)	(54)	(54)	(54)						
LEYDIG CELL ADENOMA(TA) [B]		16	16	11	10	7						

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05, **P<0.01, ***P<0.001

[B] Benign tumor
[M] Malignant tumor

Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

*** Continued

Table 22: Summary of Tumor Incidence

b(4)

02697006

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Summary of Tumor Incidence

LESIONS	TREATMENT	INCIDENCE OF TUMORS (NUMERIC)																								
		Males						Females																		
		Clean	12.5	16.25	Vehi-	Clean	12.5	16.25	Vehi-	Clean	12.5	16.25	Vehi-													
		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1			
		Air	1mg/m3	1mg/m3	1mg/m3	icle	Air	1mg/m3	1mg/m3	1mg/m3	icle	Air	1mg/m3	1mg/m3	1mg/m3	icle	Air	1mg/m3	1mg/m3	1mg/m3	icle	Air	1mg/m3	1mg/m3	1mg/m3	icle
		Contr.	189207-	189207-	189207-	Contr.	Contr.	189207-	189207-	189207-	Contr.	Contr.	189207-	189207-	189207-	Contr.	Contr.	189207-	189207-	189207-	Contr.	Contr.	189207-	189207-	189207-	Contr.
			1015	1015	1015			1015	1015	1015			1015	1015	1015			1015	1015	1015			1015	1015	1015	
PROSTATE		(54)	(54)	(54)	(54)	(54)																				
ADENOMA [B]		0	0	1	0	0																				
PREPUTIAL/(CLITORIAL) GLANDS		(1)						(1)	(2)			(1)	(1)													
Keratinizing SQUAMOUS-CELL CARCINOMA [M]		0						0	1			0	0													
ADENOMA [B]		0						1	0			0	0													
OVARIES								(56)	(56)	(56)	(56)	(56)	(56)													
GRANULOSA CELL TUMOR [M]								0	0	0	0	0	0	1												
GRANULOSA CELL TUMOR [B]								0	0	0	0	0	0	0	0											
THECOMA [B]								1	1	0	1	0	1	0	1	0										
UTERUS								(56)	(56)	(56)	(56)	(56)	(56)													
Endometrial ADENOCARCINOMA [M]								1	3	0	2	2	2													
LEIOMYOSARCOMA [M]								0	0	0	1	0	1	0												
HAEMANGIOSARCOMA [M]								1	0	0	0	0	0													
SCHWANNOMA [M]								0	0	0	1	0	0													
ADENOMA [B]								0	1	0	0	0	0													
ENDOMETRIAL STROMAL POLYP(S) [B]								11	20	20	15	17														
GLANDULAR POLYP [B]								2	0	1	0	0														
MAMMARY GLANDS		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(56)	(56)														
ADENOCARCINOMA [M]		1	1	0	0	0	1	1	0	1	0	1	0													
CARCINOMA [M], arising in fibroadenoma [M]		0	0	0	0	0	0	0	0	1	1	0	1													
FIBROADENOMA(TA) [B]		1	0	0	1	0	9	12	11	12	7															
SKIN		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	(56)	(56)														
SQUAMOUS-CELL CARCINOMA [M]		0	0	0	1	0	0	0	0	0	0	0	0													
SEBACEOUS CARCINOMA [M]		0	0	0	0	0	0	0	0	0	0	0	1													
MALIGNANT FIBROUS HISTIOCYTOMA [M]		0	0	0	0	1	0	0	0	0	0	0	0													

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05, **P<0.01, ***P<0.001
 [B] Benign tumor
 [M] Malignant tumor
 Figures in brackets represent the number of animals from which this tissue was examined microscopically
 The absence of a numeral indicates that the lesion specified was not identified

*** Continued

Table 22: Summary of Tumour Incidence

b(4)

02897006

Page: 5

Summary of Tumour Incidence

LESIONS	TREATMENT	INCIDENCE OF TUMORS (NUMERIC)									
		Males					Females				
		Clean	12.5	16.25	1Vehi-	Clean	12.5	16.25	1Vehi-		
IAir	img/m3	img/m3	img/m3	Icle	IAir	img/m3	img/m3	img/m3	Icle		
	Contr.	189207-	189207-	189207-	Contr.	Contr.	189207-	189207-	189207-	Contr.	
		1015	1015	1015			1015	1015	1015		
SKIN		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	
LIPOSARCOMA [M]		0	1	0	0	0	0	0	0	0	
HAEMANGIOSARCOMA [M]		0	0	0	0	0	1	0	0	0	
SCHWANNOMA [M]		0	0	0	0	0	0	1	0	0	
KERATOACANTHOMA [B]		0	0	0	1	0	0	0	0	0	
BASAL CELL TUMOR [B]		0	0	0	0	0	0	0	1	0	
BENIGN FIBROUS HISTIOCYTOMA [B]		1	0	0	1	1	0	0	0	0	
LIPOMA [B]		0	1	0	1	0	0	0	0	0	
HAEMANGIOMA [B]		0	1	0	0	0	0	0	0	0	
FIBROMA [B]		0	1	0	0	1	0	0	0	0	
BONE(S)						(2)		(2)	(1)		
OSTEOSARCOMA [M]						1		0	0		
SKELETAL MUSCLE		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	
HAEMANGIOSARCOMA [M]		0	0	1	0	0	0	0	0	0	
THYMUS		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	
THYMOID [B]		2	1	3	0	2	5	4	1	3	
HAEMATOP./LYMPHORET.TISSUE		(54)	(54)	(54)	(54)	(54)	(56)	(56)	(56)	(56)	
HISTIOCYTIC SARCOMA [M]		1	0	1	0	1	0	0	1	0	

Significance of difference in a pairwise Fisher's test between control and treatment groups: *P<0.05, **P<0.01, ***P<0.001
 [B] Benign tumor
 [M] Malignant tumor
 Figures in brackets represent the number of animals from which this tissue was examined microscopically
 The absence of a numeral indicates that the lesion specified was not identified

*** Listing Complete ***

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/s/

Huiqing Hao
5/24/04 05:22:13 PM
PHARMACOLOGIST

Joseph Sun
5/25/04 10:43:00 AM
PHARMACOLOGIST
I concur.

NDA 45-day Pharmacology Fileability Check List

NDA No: 21-658

Date of submission: Dec. 22, 2003

Date of 21-day fileability meeting: Feb. 9, 2004

Date of check list: Feb. 9, 2004

(1) On its face, is the Pharmacology/Toxicology section of the NDA organized in a manner to allow substantive review?

Yes (x) No ()

(2) On its face, is the Pharmacology/Toxicology section of the NDA legible for review?

Yes (x) No ()

(3) Are final reports of all required and requested preclinical studies submitted in this NDA?

	Yes	No	NA
Pharmacology	(X)	()	()
ADME	(X)	()	()
Toxicology (duration, route of administration and species specified)			
acute	(X)	()	()
subchronic and chronic studies	(X)	()	()
reproductive studies	(X)	()	()
carcinogenicity studies	(X)	()	()
mutagenicity studies	(X)	()	()
special studies	(X)	()	()
others	()	()	(X)
EA (items 7, 8, 9, 10, 11 and 15)			

(4) If the formulation to be marketed is different from the formulation used in the toxicology studies, is repeating or bridging the studies necessary? Yes (X) No ()

If no, state why not:

(5) Are the proposed preclinical labeling sections (carcinogenesis, mutagenesis and impairment of fertility, pregnancy category and overdosage) appropriate (including human dose multiples expressed in either mg/m² or comparative systemic exposure levels) and in accordance with 201.57?

Yes (X) No ()

(6) Has the applicant submitted all special studies/data requested by the Division prior to the submission including but not limited to pre-NDA discussion?

Yes (X) No () NA ()

A dog 3-month bridging study for comparing MDI and DPI has been completed.

(7) On its face, does the route of administration used in the pivotal toxicity studies appear to be the same as the intended clinical route?

Yes (X) No ()

(8) Has the applicant submitted a statement(s) that all of the toxicity studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?

Yes (X) No ()

(9) Has the applicant submitted any studies or data to address any impurity or extractable issues (if any)?

Yes (X) No ()

(10) Are there any outstanding preclinical issues?

Yes () No (X)

(11) From a preclinical perspective, is this NDA fileable?

Yes (X) No ()

If "yes", should any additional information/data be requested?

Yes () No (X)

Review Pharmacologist/Toxicologist: Huiqing Hao, Ph.D.

Team Leader: Joseph C Sun, Ph.D.

HFD-570/Division File

HFD-570/J. Shah

HFD-570/J. Sun

HFD-570/C. Jackson

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/s/

Huiqing Hao
2/26/04 12:51:04 PM
PHARMACOLOGIST

Joseph Sun
2/26/04 12:53:27 PM
PHARMACOLOGIST
I concur.

MEMORANDUM

Oct. 21, 2004

TO: File

FROM: Kenneth L. Hastings, Dr.P.H., D.A.B.T.

SUBJECT: NDA 21-658

I have reviewed the pharmacology/toxicology information provided for Alvesco (ciclesonide) Metered Dose Inhaler and concur with the recommendations by the primary reviewer, Dr. Huiqing Hao and the pharmacology/toxicology supervisor, Dr. C. Joseph Sun that the NDA is approvable. The final product label is acceptable.

Kenneth L. Hastings, Dr.P.H., D.A.B.T.

Associate Director for Pharmacology and Toxicology
Office of Drug Evaluations II & III

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/s/

Kenneth Hastings
10/21/04 04:04:56 PM
PHARMACOLOGIST

INTEROFFICE MEMO

TO: NDA 21658
FROM: C. Joseph Sun, Ph. D., Supervisory Pharmacologist (HFD-570)
DATE: September 30, 2004

I concur with pharmacologist's recommendation that pharmacology and toxicology of ciclesonide have been adequately studied and evaluated and the drug is approvable from a preclinical standpoint.

Pharmacology: The actions of ciclesonide as a pro-drug based on its major active metabolite (MR-1) activity were typical for its class and did not distinguish it from other glucocorticoids. Inhaled ciclesonide inhibited airway inflammation mediated by allergic challenge or other triggers in several animal models.

General toxicity: Chronic inhalation studies were conducted in rats (6 months) and dogs (9 months). Typical systemic glucocorticoid effects (decreases of body weights, adrenal suppression and lymphoid tissue atrophy in thymus, spleen, lymph nodes and bronchus-associated lymphoid tissue) were observed.

Reproductive toxicity: Ciclesonide did not impair fertility in rats. It was not teratogenic or embryocidal in rats but it was in rabbits. Thus, pregnancy category C is appropriate.

Genotoxicity: It was not mutagenic in an Ames test and an HGPRT forward mutation assay and was not clastogenic in a human lymphocyte assay and an in vitro micronucleus test in V79 cells. It was however clastogenic in an in vivo mouse micronucleus test.

Carcinogenicity: In two 2-year inhalation carcinogenicity studies in mice and rats, ciclesonide did not induce any tumors.

Labeling: Carcinogenesis, mutagenesis and impairment of fertility and pregnancy category C sections have been revised to incorporate the above-mentioned preclinical findings.

All issues raised during the drug development regarding its toxicities observed in chronic studies have been resolved and therefore there are no outstanding preclinical issues.

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/s/

Joseph Sun
9/30/04 04:40:14 PM
PHARMACOLOGIST

**HFD-570 DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION**

Chemistry Consult (Leachable Qualification)

NDA number: 21658

Date of submission: 10/30/2003

Request Date: 03/17/2004

Sponsor: Aventis is the sponsor of the NDA and _____ is the DMF holder

b(4)

Reviewer: Huiqing Hao, Ph.D.

Division: Division of Pulmonary and Allergy Drug Products

HFD: 570

Review Completion Date: 09/15/04

Drug: Ciclesonide MDI

Drug Class: Glucocorticoid

Indication: Asthma

Route of administration: Oral Inhalation (MDI)

Chemist Who Requested the Consult: Arthur Shaw, Ph.D.

Description of the Consult

This is a consult request to assess whether the proposed specifications for leachables in the HFA-134a ciclesonide metered dose inhaler are acceptable.

Review

The evaluation was based on the information provided in the drug master file _____ dated August 23, 2003.

b(4)

Evaluations:

The sponsor proposed the leachable specifications based on that found in _____

_____ and assumed that _____ have the same amount of leachables as that in _____ units. Target fill weights are _____ for the _____-actuation product and _____ for the _____ actuation. Based on _____ ng/actuation, total of _____ actuations can be produced by a _____ actuation product and _____ actuations by a _____ actuation product. Maximally _____ actuations per day are recommended for the drug product. The maximum daily exposure of each leachable was calculated as Leachable amount (ng/unit) _____ actuations/unit × _____ actuations/day.

b(4)

1. _____ leachables:

Maximum _____ concentrations in the samples (HFA134a Ciclesonide MDI Placebo Formulation) were as listed in the following table. Specifications of _____ was proposed for _____ only.

b(4)

4 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Huiqing Hao
9/15/04 11:33:03 AM
PHARMACOLOGIST

Joseph Sun
9/15/04 11:45:45 AM
PHARMACOLOGIST
I concur.