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69db5d07-5f49-4c20-8681-fbfd261e09c6

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Type at least 3 characters

OECD Exchange of experimental data
NDA203188-ivacaftor

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1 2 0

Administrative data | Data source | Materials and methods | Results and discussion | Overall remarks, attachments | Applicant's summary and conclusion

Administrative data

Endpoint
carcinogenicity: oral

Type of information
experimental study

Adequacy of study

☐ Robust study summary

☐ Used for classification

☐ Used for SDS

Study period

Reliability

Rationale for reliability incl. deficiencies

Data waiving

Justification for data waiving

Justification for type of information

Attached justification

Attached justification Reason / purpose Actions

Cross-reference

Reason / purpose for cross-reference Related information Remarks Actions

Data source

Reference

Data access

Data protection claimed

Materials and methods

Test guideline

Qualifier Guideline Version / remarks Deviations Actions

Principles of method if other than guideline

GLP compliance

Test material

Test material information

- NDA203188_TM1 | ivacaftor | (N-(2,4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3- carboxamide) | 873054-44-5

Additional test material information

Specific details on test material used for the study
Drug, lot #, and % purity: VX-770, Lot # 17QB02.HQ00016, 100% pure

Specific details on test material used for the study (confidential)

Test animals

Species
mouse

Strain
CD-1

Details on species / strain selection
Albino Mice (Outbred) VAF/Plus Crl:CD-1 9ICR)BR

Sex
male/female

Details on test animals or test system and environmental conditions
Age: 7 to 8 weeks at initiation of dosing

Administration / exposure

Route of administration
oral: gavage

Type of inhalation exposure (if applicable)

Vehicle
other: 0.5% w/v methylcellulose (MC) with 0.5% w/v sodium lauryl sulfate (SLS) in water

[default] : 0.5% w/v methylcellulose (MC) with 0.5% w/v sodium lauryl sulfate (SLS) in water

Mass median aerodynamic diameter (MMAD)

Geometric standard deviation (GSD)

Remarks on MMAD

Details on exposure

Analytical verification of doses or concentrations

Details on analytical verification of doses or concentrations

Duration of treatment / exposure
24 months

Frequency of treatment
once daily

Post exposure period
not specified

Doses / concentrations

Dose / conc. Remarks Actions 1
Dose / conc.
25 mg/kg bw/day (actual dose received)
Remarks
2
Dose / conc.
75 mg/kg bw/day (actual dose received)
Remarks
3
Dose / conc.
mg/kg bw/day (actual dose received)
Remarks
4
Dose / conc.
200 mg/kg bw/day (actual dose received)
Remarks

No. of animals per sex per dose
Main Study: 65/sex/group TK: 54/sex/group

Control animals

Details on study design
Methods Doses: 0 (Vehicle 1), 0 (Vehicle 2), 25, 75, 200 mg/kg/day Frequency of dosing: Once daily, 7 days/week for up to 24 months Dose volume: 5 mL/kg Route of administration: oral intubation (gavage) Formulation/Vehicle: Test article was a 50:49.5:0.5 mixture of VX-770 and hydroxypropylmethylcellulose acid succinate (HPMC-AS) and sodium lauryl sulfate (SLS). The powder was formulated as a suspension in Vehicle 1; Vehicle 1: 0.5% w/v methylcellulose (MC) with 0.5% w/v sodium lauryl sulfate (SLS) and 0.01% w/v simethicone in water (all test article groups were dosed in Vehicle 1); Vehicle 2: 0.5% w/v methylcellulose (MC) with 0.5% w/v sodium lauryl sulfate (SLS) in water Basis of dose selection: The MTD established for chronic oral administration in mice was believed to be <300 mg/kg/day, based on results of a 3-month study (08-2051, VX-770-TX-012). After 3 months of dosing, the 1000 and 600 mg/kg/day doses were associated with excessive test article-related mortality. Species/Strain: Albino Mice (Outbred) VAF/Plus Crl:CD-1 9ICR)BR Number/Sex/Group: Main Study: 65/sex/group TK: 54/sex/group Age: 7 to 8 weeks at initiation of dosing Animal housing: Animals were pair-housed in stainless steel, wire mesh cages during the

initial week of stabilization (at least 7 days). Animals were housed individually in suspended stainless steel wire mesh cages thereafter. An enrichment device (e.g. Nylabone) was provided in each animal's cage at all times. Paradigm for dietary restriction: None Dual control employed: No. However, Vehicle control 2 (without simethicone, see above) was included since there was no data available from 2-yr studies with vehicle containing simethicone Interim sacrifice: None Satellite groups: TK: 54/sex/group Deviation from study protocol: No significant deviations occurred; however, due to an error in the original study protocol test article concentrations for the low- and high- dose groups, animals in these groups received 50% less than the intended concentration (and therefore 50% less than the intended dose) during Month 1 of the study. The error was corrected in Amendment 1 to the study protocol. The sponsor considers that this did not have an impact on the study, since low- and high-dose animals received the correct test article concentrations from Months 2-24, the majority of the study/animal lifespan.

Positive control

Examinations

Observations and examinations performed and frequency

Sacrifice and pathology

Other examinations

Statistics

Any other information on materials and methods incl. tables

Results and discussion

Results of examinations

Clinical signs

Description (incidence and severity)
Clinical Signs Cage-side observations for poor health or toxic or pharmacologic effects (eg. abnormalities in general condition, appearance, activity, behavior, respiration, etc.) were performed once daily. Physical examinations (e.g. general condition, skin and fur, eyes, nose, oral cavity, abdomen and external genitalia, as well as palpation of masses and evaluations of respiration) were performed twice pretest and weekly during the study period. An increased incidence of moist rales was observed in high-dose males and females versus controls during both cage-side observations and physical exams. An increased incidence of labored breathing was observed in high-dose males and females during cage-side observations and in high-dose males during physical exams versus controls. Other test article-related clinical signs noted during cage-side observations included an increased incidence of body cold to touch in high-dose males, and decreased fecal volume and piloerection in low-, mid-, and high-dose males versus controls. Other test article-related clinical signs observed during physical exams included decreased activity in high-dose males and ocular lacrimation in high-dose females versus controls.

Dermal irritation (if dermal study)

Description (incidence and severity)

Mortality

Description (incidence)
Mortality Cage-side observations for mortality/morbidity were performed twice daily. There were no statistically significant differences in mortality between control and test article groups. Among main study animals, there were 409 early decedents out of a total of 650 mice (62.9%). The distribution of early decedents (found dead or morbid sacrifice) versus animals surviving at termination is summarized below.

Body weight and weight changes

Description (incidence and severity)

Food consumption and compound intake (if feeding study)

Description (incidence and severity)

Food efficiency

Description (incidence and severity)

Water consumption and compound intake (if drinking water study)

Description (incidence and severity)

Ophthalmological findings

Description (incidence and severity)

Haematological findings

Description (incidence and severity)

Clinical biochemistry findings

Description (incidence and severity)

Endocrine findings

Description (incidence and severity)

Urinalysis findings

Description (incidence and severity)

Behaviour (functional findings)

Description (incidence and severity)

Immunological findings

Description (incidence and severity)

Organ weight findings including organ / body weight ratios

Description (incidence and severity)

Gross pathological findings

Description (incidence and severity)

Neuropathological findings

Description (incidence and severity)

Histopathological findings: non-neoplastic

Description (incidence and severity)
Test article-related non-neoplastic findings included an increased incidence of mineralization in the bicep and heart in high-dose females, as well as an increased incidence of arteritis/periarteritis +/- fibrinoid degeneration in the heart and vessel in high-dose females.

Histopathological findings: neoplastic

Description (incidence and severity)

Other effects

Description (incidence and severity)

Details on results
Observations and Results Mortality Cage-side observations for mortality/morbidity were performed twice daily. There were no statistically significant differences in mortality between control and test article groups. Among main study animals, there were 409 early decedents out of a total of 650 mice (62.9%). The distribution of early decedents (found dead or morbid sacrifice) versus animals surviving at termination is summarized below. Marcie Wood, Ph.D. Clinical Signs Cage-side observations for poor health or toxic or pharmacologic effects (eg. abnormalities in general condition, appearance, activity, behavior, respiration, etc.) were performed once daily. Physical examinations (e.g. general condition, skin and fur, eyes, nose, oral cavity, abdomen and external genitalia, as well as palpation of masses and evaluations of respiration) were performed twice pretest and weekly during the study period. An increased incidence of moist rales was observed in high-dose males and females versus controls during both cage-side observations and physical exams. An increased incidence of labored breathing was observed in high-dose males and females during cage-side observations and in high-dose males during physical exams versus controls. Other test article-related clinical signs noted during cage-

side observations included an increased incidence of body cold to touch in high-dose males, and decreased fecal volume and piloerection in low-, mid-, and high-dose males versus controls. Other test article-related clinical signs observed during physical exams included decreased activity in high-dose males and ocular lacrimation in high-dose females versus controls. Body Weights Body weights were recorded twice pretest, weekly through 13 weeks, every 4 weeks thereafter (non-fasting), and at termination. There were no statistically significant Reference ID: 3066492 differences in body weight between control and test article groups over the study duration. Feed Consumption Feed was available without restriction 7 days/week. Food consumption was measured (weighed) at pretest, weekly through 13 weeks, and every 4 weeks thereafter. There were no consistent test article-related effects on food consumption in VX-770-treated males or females versus controls during the study duration. Gross Pathology Necropsies were performed on all surviving main study animals (unfasted) after at least 24 months of dosing. Complete macroscopic exams were performed on all main study animals, including animals sacrificed prior to study termination. There were no test article-related macroscopic findings. Histopathology Peer Review: A peer review was not performed. Neoplastic No statistically significant, test article-related neoplastic findings were observed in mice. Non-statistically significant findings included a dose-related increase in harderian gland adenoma/carcinoma in female mice and an increase in benign interstitial cell tumors in the testes of high-dose males. Group 1: 0 mg/kg/day (vehicle with simethicone) Group 2: 0 mg/kg/day (vehicle without simethicone) Group 3: 25 mg/kg/day Group 4: 75 mg/kg/day Group 5: 200 mg/kg/day Non Neoplastic Test article-related non-neoplastic findings included an increased incidence of mineralization in the bicep and heart in high-dose females, as well as an increased incidence of arteritis/periarteritis +/- fibrinoid degeneration in the heart and vessel in high-dose females. Reference ID: 3066492 Toxicokinetics Blood samples were obtained to determine plasma concentrations of VX-770 and major metabolites M1 (hydroxymethyl-VX-770) and M6 (VX-770 carboxylate). Blood samples (0.5 mL) were obtained from anesthetized animals via retrobulbar orbital sinus on Day 1 and at the end of Months 6 and 12, as shown in the following table: Results of TK analyses for VX-770, M1, and M6 in mice are presented in Tables 7-9 below. At Month 12 (steady-state), increases in AUC0-24hr for VX-770 were approximately dose-proportional from 25 to 75 mg/kg/day and 75 to 200 mg/kg/day in females. In males, AUC0-24hr for VX-770 increased in a greater than dose-proportional manner from 25 to 75 mg/kg/day (~10x) and did not increase from 75 to 200 mg/kg/day. Increases in AUC0- 24hr for VRT-837018 (M1) were slightly less than dose-proportional from 25 to 75 mg/kg/day and 75 to 200 mg/kg/day in females. In males, AUC0-24hr for M1 did not increase from 25 to 75 mg/kg/day and increased in an approximately dose-proportional manner from 75 to 200 mg/kg/day. Increases in AUC0-24hr for VRT-842917 (M6) were less than dose proportional from 25 to 75 mg/kg/day and slightly greater than dose-proportional from 75 to 200 mg/kg/day in females. In males, AUC0-24hr for M6 decreased (~3x) from 25 to 75 mg/kg/day and increased (~4.5x) from 75 to 200 mg/kg/day. In general, systemic exposure (AUC0-24hr) of VX-770 and metabolites VRT-837018 (M1) and VRT-842917 (M6) was greater in females than males at most time points (Day 1, Month 6 and Month 12). Also at Month 12, AUC0-24hr of VRT-837018 (M1) reached a maximum of 69% of VX-770 exposure (low-dose males) and AUC0-24hr of VRT-842917 (M6) reached a maximum of 12% of VX-770 exposure (low-dose males). Accumulation of VX-770, M1, and M6 was observed in mid-dose males and females from Day 1 to Months 6 and 12 and in all dose groups from Months 6 to 12. Table 8: Summary of TK parameters on Day 1, Month 6, and Month 12 for VX-770 in female and male mice following once daily oral administration of 25, 75, and 200 mg/kg/day of VX-770 Dosing Solution Analysis Homogeneity and dose confirmation analyses on Days 1, 182, 363, 372, 470, 523, 644, and 728 of the study demonstrated that the mixing procedure produced homogenous batches and confirmed that dosing formulations of the appropriate concentration were administered.

Relevance of carcinogenic effects / potential
Evaluation of Tumor Findings No test article-related neoplastic findings were observed in mice.

Effect levels

Key result Dose descriptor Effect level Based on Sex Basis for effect level Remarks on result Actions 1

☐ Key result
Dose descriptor
NOAEL
Effect level
Based on
Sex
male/female
Basis for effect level

Remarks on result
other: Not reported by medical writer

[default] : Not reported by medical writer

2

☐ Key result
Dose descriptor
dose level:
Effect level
200 mg/kg bw/day (actual dose received)
Based on
Sex
female
Basis for effect level

- histopathology: non-neoplastic

Remarks on result
3
☐ Key result
Dose descriptor
NOEL
Effect level
<= 200 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- body weight and weight gain

Remarks on result
4
☐ Key result
Dose descriptor
NOEL
Effect level
<= 200 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- food consumption and compound intake

Remarks on result
5
☐ Key result
Dose descriptor
NOEL
Effect level
<= 200 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- gross pathology

Remarks on result
6
☐ Key result
Dose descriptor
dose level:
Effect level
200 mg/kg bw/day (actual dose received)
Based on
Sex
female
Basis for effect level

- histopathology: non-neoplastic

Remarks on result
7
☐ Key result
Dose descriptor
NOEL
Effect level
<= 200 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- histopathology: neoplastic

Remarks on result
8
☐ Key result
Dose descriptor
dose level:
Effect level
200 mg/kg bw/day (actual dose received)
Based on
Sex
female
Basis for effect level

- histopathology: non-neoplastic

Remarks on result
9
☐ Key result
Dose descriptor
dose level:
Effect level
200 mg/kg bw/day (actual dose received)
Based on
Sex
female
Basis for effect level

- histopathology: non-neoplastic

Remarks on result
10
☐ Key result
Dose descriptor
dose level:
Effect level
200 mg/kg bw/day (actual dose received)
Based on
Sex
female
Basis for effect level

- histopathology: non-neoplastic

Remarks on result
11
☐ Key result
Dose descriptor
NOEL
Effect level
<= 200 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- mortality

Remarks on result
12
☐ Key result
Dose descriptor
dose level:
Effect level
200 mg/kg bw/day (actual dose received)
Based on

Sex
female
Basis for effect level

- histopathology: non-neoplastic

Remarks on result

Target system / organ toxicity

Key result Critical effects observed Lowest effective dose / conc. System Organ Treatment related Dose response relationship Relevant for humans Actions

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Any other information on results incl. tables

Overall remarks, attachments

Overall remarks

Attachments

Type Attached (confidential) document Attached (sanitised) documents for publication Remarks Actions

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Illustration (picture/graph)

Applicant's summary and conclusion

Conclusions

Executive summary
Key Study Findings tNo test article-related effects on mortality, body weight, food consumption, or macroscopic findings were observed versus controls. tNo statistically significant, test article-related neoplastic findings were observed. tNon-neoplastic microscopic findings included an increased incidence of mineralization of the bicep and heart and an increased incidence of arteritis/periarteritis +/- fibrinoid degeneration in the heart and vessel in high-dose females. tAccumulation of VX-770 and metabolites M1 and M6 was observed in males and females by Months 6 and 12. In addition, systemic exposure of VX-770, M1, and M6 was generally greater in females than males. Adequacy of Carcinogenicity Study Concurrence for the dose levels used in the study was obtained from the ECAC (See ECAC meeting summary dated January 27, 2009). The duration of treatment (104 weeks) in mice was adequate. Appropriateness of Test Models This was a 2-year carcinogenicity study in mice in which test article was administered by the oral route. This is the same route to be used in the clinical setting in which humans will receive chronic, daily doses of VX-770. Evaluation of Tumor Findings No test article-related neoplastic findings were observed in mice.

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