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dossier created for substance NDA204790-dolutegravir

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View Dossiers Validate

- Export to i6z
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- Create component PDF/RTF
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Type at least 3 characters

OECD Exchange of experimental data
NDA204790-dolutegravir

- 1 General information
  1
- 2 Classification and Labelling
- 4 Physical and chemical properties
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  - 7.1 Toxicokinetics, metabolism and distribution
  - 7.2 Acute Toxicity
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- 7.7 Carcinogenicity
  2
    - Carcinogenicity Study (gavage) of S-349572 sodium in Rats for 104 Weeks_2
    - Carcinogenicity Study (Gavage) of S-349572 Sodium in Mice for 104 Weeks_09-2177
  - 7.8 Toxicity to reproduction
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- Compare Document

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

- NDA204790_TM1 | Dolutegravir | Sodium (4R,9aS)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8adiazaanthracene-7-carboxylic acid 2,4-difluorobenzylamide | 1051375-19-9 (Na salt)

Additional test material information

Specific details on test material used for the study
Drug, lot #, and % purity: S-349572 sodium, lot B86001 (98.9%), lot 091001 100.1%

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

Test animals

Species
rat

Strain
Sprague-Dawley

Details on species / strain selection

Sex
male/female

Details on test animals or test system and environmental conditions
Age: Approximately 7 weeks Animal housing: Animals were pair housed in elevated, stainless steel, wire mesh cages during the first week of the stabilization period and individually housed thereafter.

Administration / exposure

Route of administration
oral: gavage

Type of inhalation exposure (if applicable)

Vehicle
other: Solution/Aqueous 0.5 w/w% hydroxypropyl methylcellulose (HPMC) solution with 0.1 w/w% Tween 80 (0.5% HPMC/0.1% Tween 80)

[default] : Solution/Aqueous 0.5 w/w% hydroxypropyl methylcellulose (HPMC) solution with 0.1 w/w% Tween 80 (0.5% HPMC/0.1% Tween 80)

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
104 weeks

Frequency of treatment
once daily

Post exposure period
not specified

Doses / concentrations

Dose / conc. Remarks Actions 1
Dose / conc.
10 mg/kg bw/day (actual dose received)
Remarks
2
Dose / conc.
mg/kg bw/day (actual dose received)
Remarks
3
Dose / conc.
50 mg/kg bw/day (actual dose received)
Remarks
4
Dose / conc.
2 mg/kg bw/day (actual dose received)
Remarks

No. of animals per sex per dose
65/sex/group

Control animals

Details on study design
Methods Doses: 0 (water) or 0 (0.5% HPMC/0.1% Tween 80), 2, 10, or 50 mg/kg/day Frequency of dosing: Once daily Dose volume: 10 mL/kg/day Route of administration: Oral gavage Formulation/Vehicle: Solution/Aqueous 0.5 w/w% hydroxypropyl methylcellulose (HPMC) solution with 0.1 w/w% Tween 80 (0.5% HPMC/0.1% Tween 80) Basis of dose selection: In the 6-month study in rats, the difference in exposure levels between the 500 mg/kg/day dose group and the 50 mg/kg/day dose group was as little as 2 fold; therefore, based on a dosing period of 104 weeks for this study a high dosage of 50 mg/kg/day was chosen as the maximally tolerated dose. Species/Strain: Rats/Sprague-Dawley

Number/Sex/Group: 65 Age: Approximately 7 weeks Animal housing: Animals were pair housed in elevated, stainless steel, wire mesh cages during the first week of the stabilization period and individually housed thereafter. Paradigm for dietary restriction: Not applicable Dual control employed: Yes Interim sacrifice: No Satellite groups: Toxicokinetics Deviation from study protocol: Due to the dose formulation batch size requirements necessitating the preparation of 2 batches, single samples from each batch were sampled and analyzed rather than the protocol required duplicate samples from a single batch. The Week 1 homogeneity and dose concentration did not meet the protocol acceptance criteria (±10% of the nominal concentration) and was therefore reformulated. The Group 3, 14 day refrigerated stability analysis concentration (82.3%) was not within the protocol specified criteria of within ±10% of the initial Group 3 concentration (98.8%).

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)

Dermal irritation (if dermal study)

Description (incidence and severity)

Mortality

Description (incidence)

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)

Histopathological findings: neoplastic

Description (incidence and severity)

Other effects

Description (incidence and severity)

Details on results

Relevance of carcinogenic effects / potential
Evaluation of Tumor Findings No tumor incidences satisfied the appropriate criteria to be described as statistically significant.

Effect levels

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

☐ Key result
Dose descriptor
NOEL
Effect level
<= 50 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- food consumption and compound intake

Remarks on result
2

☐ Key result
Dose descriptor

NOEL
Effect level
<= 50 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- gross pathology

Remarks on result
3
☐ Key result
Dose descriptor
NOEL
Effect level
<= 50 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- histopathology: neoplastic

Remarks on result
4
☐ Key result
Dose descriptor
NOEL
Effect level
<= 50 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- mortality

Remarks on result
5
☐ Key result
Dose descriptor
NOEL
Effect level
<= 50 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- body weight and weight gain

Remarks on result
6
☐ Key result
Dose descriptor
NOEL
Effect level
<= 50 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- clinical signs

Remarks on result
7
☐ Key result
Dose descriptor

NOEL
Effect level
<= 50 mg/kg bw/day (actual dose received)
Based on
Sex
Basis for effect level

- histopathology: non-neoplastic

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

- other: Not reported by medical writer

  [default] : Not reported by medical writer

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 tS-349572 administered orally by gavage to rats at doses of 2, 10 and 50 mg/kg/day for up to 2 years had no effect on survival and was not carcinogenic. tThe no observed adverse effect level (NOAEL) for non-neoplastic findings after chronic oral administration was the high dose of 50 mg/kg/day. tThe steady state (Day 182) AUCo-24h values for the high dose groups were 713 and 1140 Hg.li/mL for males and females, respectively, which were 13-fold and 21-fold the mean estimated steady-state human AUCo-24h of 54 pg.h/mL (50 mg qd to adults), respectively. Adequacy of Carcinogenicity Study The doses used for this study were appropriately selected based on MTD and saturation of absorption. Appropriateness of Test Models CD Sprague Dawley rats are an appropriate animal model. Evaluation of Tumor Findings No tumor incidences satisfied the appropriate criteria to be described as statistically significant.

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