CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
Benzovindiflupyr

Chemical Code # 6113, Document Processing Number (DPN) # 53206
SB 950 # NA
10/4/13
Revised 10/20/14

DATA GAP STATUS

Chronic toxicity, rat: No data gap, no adverse effect indicated
Chronic toxicity, dog: No data gap, no adverse effect indicated
Oncogenicity, rat: No data gap, possible adverse effect
Oncogenicity, mouse: No data gap, no adverse effect indicated
Reproduction, rat: No data gap, no adverse effect indicated
Developmental toxicity, rat: No data gap, no adverse effect indicated
Developmental toxicity, rabbit: No data gap, no adverse effect indicated
Gene mutation: No data gap, no adverse effect indicated
Chromosome effects: No data gap, no adverse effect indicated
DNA damage: No data gap, no adverse effect indicated
Neurotoxicity: Data gap

Toxicology one-liners are attached.

All record numbers for the above study types through 272081 (Document No. 53206-0068) were examined. This includes all relevant studies indexed by DPR as of 10/4/13.

In the 1-liners below:
**indicates an acceptable study.
**Bold face** indicates a possible adverse effect.
File name: T141020
Revised by T. Moore, 10/4/13, H. Green, 10/20/14.

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

**Table of Contents**

METABOLISM AND PHARMACOKINETICS ................................................................. 3

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT ........................................ 7
  Acute oral toxicity, rat ............................................................................................... 7
  Acute dermal toxicity ............................................................................................... 7
  Acute inhalation toxicity, rat ..................................................................................... 7
  Primary eye irritation, rabbit .................................................................................. 8
  Primary dermal irritation ......................................................................................... 8
  Dermal sensitization ............................................................................................... 8

SUBCHRONIC STUDIES (units of mg/kg/day unless specified) ................................ 8
  Oral toxicity, rat: ........................................................................................................ 8
  Oral toxicity, non-rodent: ....................................................................................... 11
  Dermal toxicity, 21/28-day or 90-day: ................................................................... 11

CHRONIC STUDIES .................................................................................................. 12
  Chronic, rat .............................................................................................................. 12
  Chronic, dog ............................................................................................................ 12
  Oncogenicity, rat ..................................................................................................... 12
  Oncogenicity, mouse .............................................................................................. 13

GENOTOXICITY ........................................................................................................... 13
  Gene mutation ...................................................................................................... 13
  Chromosome damage ........................................................................................... 14
  DNA damage or miscellaneous effects ................................................................... 14

REPRODUCTIVE TOXICITY, RAT .......................................................................... 15

DEVELOPMENTAL TOXICITY .................................................................................. 16
  Rat .......................................................................................................................... 16
  Rabbit ...................................................................................................................... 17

NEUROTOXICITY ...................................................................................................... 17
  Acute, rat ............................................................................................................... 17
  90-day, rat ............................................................................................................ 17
Developmental neurotoxicity, rat ................................................................. 17
Delayed neurotoxicity, hen ........................................................................... 17

IMMUNOTOXICITY ....................................................................................... 18
ENDOCRINE DISRUPTOR STUDIES ............................................................. 18
SUPPLEMENTAL STUDIES ......................................................................... 18

METABOLISM AND PHARMACOKINETICS

Metabolism, Rat
53206-0005; 270564; “SYN545192 – Analysis of SYN545192 and Its Metabolites from Dietary Studies in Rats”; (C. Laver; Charles River, Tranent, Edinburgh, EH33 2NE, UK; Study No. 309700; 2/25/11); Serum samples derived from study animals which had received 0, 100, 750, or 1500 ppm of SYN545192 (benzovindiflupyr technical) (batch no. TE-6341; purity: 98.3%) in the diet for either 28 days (study no. 459287) (vol. no. 53206-0048; rec. no. 270707) (consumption of a.i. was not calculated for the report) or 90 days (study no. 459292) (vol. no. 53206-0041; rec. no. 270685) ((M) 0, 7.6, 53.8, 108.7 mg/kg/day, (F) 0, 8.2, 58.8, 108.8 mg/kg/day) were analyzed for the presence of the parent compound and/or metabolites. In the shorter study, serial sacrifices of 5 animals/sex/group/time point were performed on study days 3, 4, 8, 15 and 29. Blood samples were collected at the time of euthanasia for analysis. In the subchronic study, on study day 79, blood was drawn from the tail vein of each animal at 0600, 1100 and 1800 hours during the time when the animals were fasting. Over the course of the 28 days of treatment, serum levels of the parent compound and/or specific metabolites were shown to increase, particularly for the females (approximately 2x). However, the concentrations of the respective compounds in the serum on study day 79 were less than those noted after 28 days of treatment so that the apparent sequestration of the test material and metabolites did not persist. The concentrations of the parent compound and metabolites in the serum on study day 79 gradually diminished over the 12-hour fasting period. The concentrations of the metabolites were generally greater in the females than the males, especially the desmethyl-SYN545192 concentration which ranged between 5 and 10 times greater than the levels in the males. One note of caution must be expressed. The concentrations of the desmethyl hydroxyl dehydrated-SYN545192 reported in the 28-day study were approximately 10 fold greater than those noted in the subchronic study. Study supplemental. (Moore, 7/15/13)

53206-0005; 270570; “SYN545192 – The Pharmacokinetics of [Pyrazole-14C]-SYN545192 in the Rat Following Single Oral Administration”; (J. Shaw, E. Montgomery; Charles River, Tranent, Edinburgh, EH33 2NE, UK; Study No. 190819; 8/10/11); Nine Wistar rats/sex/group were dosed orally by gavage with 1.0 or 40 mg/kg of [Pyrazole-14C]-SYN545192 (batch no. 5072PJS001-2, specific activity: 147.5 uCi/mg, radiochemical purity: 97.9%). Unlabeled SYN545192 (batch no. SMU9BP005, purity: 97.0%) was used to adjust the specific activity of the dosing preparations. A pharmacokinetic study was performed in which blood was collected from the tail vein of 3 animals/sex/group at specified time points up to 120 hours post-dose. An excretion balance study was performed in which 3 animals/sex/group were maintained in metabolism cages and urine and feces samples were recovered up to 120 hour post-dose. In the pharmacokinetic study, the time to peak plasma and blood concentrations ranged from 4 to 6 hours over the treatment range for the males. For the females, the time to peak levels for
plasma and blood were 2 and 4 hours for the 1.0 treatment group and was 24 hours for the 40 mg/kg treatment, respectively. The t1/2 values for the plasma and blood of the males were 55 and 62 hours at 1.0 mg/kg and 30 and 34 hours at 40 mg/kg, respectively. For the females, the t1/2 values were 29 and 27 hours and 33 and 28 hours for the plasma and blood at 1.0 and 40 mg/kg, respectively. The overall Cmax values were slightly greater for the males in comparison to those of the females at both treatment levels. In the excretion balance study, the test material was largely excreted in the feces with 89% of the administered dose being recovered in the 1.0 mg/kg treatment group and 95% being recovered in the 40 mg/kg group. The total of the administered dose recovered in the urine ranged from 4.9 to 8.9%. The percentage which was absorbed could not be determined. Study supplemental (only a portion of the data requirements for a rat metabolism study were fulfilled) (Moore, 5/20/13)

53206-0005; 270572; “SYN545192 – An Investigation of the Tissue Distribution (QWBA) of Total Radioactivity in the Rat Following Oral Administration of Pyrazole or Phenyl Labelled [14C]-SYN545192”; (J. Shaw; Charles River, Tranent, Edinburgh, EH33 2NE, UK; Study No. 190473; 8/12/11); Two Wistar rats/sex/group were dosed orally by gavage with 1 or 40 mg/kg of either [Pyrazole-5-14C]-SYN545192 (batch no. 5052PJS001-1, specific activity: 148.8 uCi/mg, radiochemical purity: 98.2%) or [Phenyl-U-14C]-SYN545192 (batch no. 5051GAR006-4, specific activity: 149.0 uCi/mg, radiochemical purity: 98.8%). Unlabeled SYN545192 (batch no. TE-6341, purity: 98.3%) was used to adjust the specific activity of the dosing preparation. One animal/sex/group was euthanized at 1 or 5 hours post-dose and the remaining animal/sex/group was euthanized at 72 hours post-dose (Note: two of the females in the 40 mg/kg group were euthanized in extremis at 5 hours rather than at 8 hours as planned). Their bodies were immediately frozen. Three sagittal sections of at least 30 um were cut and the sections were exposed to phosphor screens for 7 days. Particular controls were instituted to provide a quantitative comparison. Although the radiolabel was extensively distributed throughout the body by the 1 to 5 hour time point post-dose, the radiolabel was predominately present in the gastrointestinal tract and liver, particularly at the higher treatment level. At 72 hours post-dose, the large intestine and liver were still prominent sites of sequestration. However, the Harderian gland, kidneys, adrenal gland and brown fat were also notable for their higher concentrations of the radiolabel. There was no particular difference in the distribution of radiolabel between the two test materials. Collection of carbon dioxide from the animals in the 1 mg/kg treatment groups demonstrated that 0.01 to 0.03% of the administered dose was recovered up to 24 hours post-dose. This study was performed as a preliminary evaluation of tissue distribution for the test material. Study supplemental. (Moore, 5/23/13)

53206-0005; 270573; “SYN545192 – The Biliary Elimination of Total Radioactivity in the Rat Following Single Oral Administration of [Pyrazole-14C]-SYN545192”; (J. Shaw; Charles River, Tranent, Edinburgh, EH33 2NE, UK; Study No. 190824; 8/12/11); Four bile-duct catheterized Wistar rats/sex/group were dosed orally by gavage with 1 or 40 mg/kg of [Pyrazole-5-14C]-SYN545192 (batch no. 5107PJS001-1, specific activity: 150.0 uCi/mg, radiochemical purity: 97.7%). Urine, feces and bile were collected at specified time intervals up to 48 hours post-dose. Sixty eight to 76% of the administered dose was recovered in the bile by 48 hours post-dose for the 1 mg/kg treatment group. This percentage declined to 45 to 57% of the dose for the 40 mg/kg treatment group. The percentage recovered in the urine and feces ranged from 3.5 to 4% and from 16 to 17%, respectively for the 1 mg/kg treatment group and from 4 to 9% and from 32 to 33%, respectively for the 40 mg/kg treatment group. The percentage of the administered dose which was absorbed was 79 to 81% for the 1 mg/kg treatment group and 60 to 62% for the 40 mg/kg group. Study supplemental. (Moore, 5/23/13)
**SYN545192 – The excretion and tissue distribution of \([^{14}\text{C}]\)SYN545192 in the rat following single oral administration**; (Shaw, J., Combe, D., Montgomery, E.; Report no. 30575, study No. 190845; 8/12/11); Groups of 4 male and 4 female Han Wistar rats were exposed to a single oral dose of 1 mg or 40 mg \([\text{pyrazole-5-}^{14}\text{C}]\)-SYN545192/kg (Batch no.: S072PJS001-2, specific activity: 1 mg/kg: 5.46 MBq/mg (147.5 uCi/mg); 40 mg/kg: 0.125 MBq/mg (3.38 uCi/mg), radiochemical purity: 97.9%), in 1% aqueous carboxymethylcellulose (CMC) containing 0.1% Tween 80. The rats were investigated for excretion over seven days and for tissue distribution of radioactivity. The major route of elimination for the low and high dose administration was via feces, with more than 80% of the administered radioactivity recovered by day 7 in males and females. (84.1% for males of 1 mg/kg, 90.4% for females after 1 mg/kg, 92.7% for males at 40 mg/kg, 90.3% for females after 40 mg/kg). The excretion in urine and feces was rapid, with higher than 90% excreted within 72 hours following administration. The residues of radioactivity in the carcass or GI tract and content were low but detectable 7 days after the oral exposure of both 1 mg/kg and 40 mg/kg doses. The tissue distribution was similar in both sexes at both doses, with kidneys and liver having the highest concentrations. **Supplemental.** (Pan & Leung, 6/21/13)

**SYN545192 – Investigation of the nature and identity of radiolabelled metabolites present in urine, feces, bile and plasma collected from rats following oral administration of \([^{14}\text{C}]\)SYN545192**; (Green, M., MacDonald, M.; Report no. 31096, study No. 214808; 8/31/11); Metabolites from feces, urine, bile and plasma samples collected from male and female rats and bile duct cannulated rats which were exposed to a single oral dose of 1 mg or 40 mg \([\text{pyrazole-5-}^{14}\text{C}]\)-SYN545192/kg, as well as from male rats given 14 consecutive daily oral doses (1 mg/kg \([\text{pyrazole-5-}^{14}\text{C}]\)-SYN545192/kg) were identified. In feces, the major metabolites from non-cannulated rats were hydroxylated metabolites of both SYN545192 and SYN546206. A sulphate conjugate of SYN 546042 in female and ring open metabolites in males were detected. Feces from bile duct cannulated rats contained only SYN545192 and SYN546039 with some conjugates. In urine, the major metabolites from non-cannulated rats were hydroxylated metabolites of both SYN545192 and SYN546206 with some conjugates. A sulphate conjugate of SYN 546042 in female and ring open metabolites in males were detected. Urines from bile duct cannulated rats had similar metabolites as from non-cannulated rats, with SYN546041 glucuronide being the major metabolite. Metabolites in bile were glucuronide conjugates of hydroxylated metabolites of SYN545192 and SYN546206. Major metabolites were SYN546041, SYN546360 and SYN546039. The plasma samples collected at Tmax contained SYN545192 and hydroxylated metabolites of SYN545192 and SYN546206. Major metabolites in males were SYN546041, SYN545192, SYN546039, SYN546042 and low concentration of SYN546206. There were evidence suggesting that the radioactivity was associated with plasma proteins and were partially solubilized in more aqueous extracts. The major metabolite in plasma from females was SYN546206. Overall, there were at least 8 types of metabolites: desmethyl, hydroxy, dihydroxy, desmethyl hydroxy, desmethyl dihydroxy, ring-open, glucuronide conjugate, and sulphate conjugate. Majority of the administered radioactivity (70-85%) was identified as SYN 546041, SYN546360, SYN546643, SYN546645 and SYN546619. No significant differences were observed following a single dose of 1 mg/kg or 40 mg/kg or repeat daily dose of 1 mg/kg. Minor differences between metabolites from males (ring open metabolites) and females (sulphate conjugates) were observed. Possible cleavage products of SYN545192 between the pyrazole and phenyl moieties were present in urine only at < 2% dose. **Supplemental.** (Pan & Leung, 6/25/13)

**SYN545192 – The tissue depletion of \([\text{pyrazole-}^{14}\text{C}]\)SYN545192 in the rat following single oral administration**; (Hutton, E. and Shaw, J.; Report no. 30698, study No. 190850; 11/7/12); 1 mg/kg or 40 mg/kg \([\text{pyrazole-}^{14}\text{C}]\)-SYN545192 (Batch no.:
5072PJS001-2, specific activity: 1 mg/kg: 5.46 MBq/mg (147.5 uCi/mg); 40 mg/kg: 0.118 MBq/mg, radiochemical purity: 97.9%, unlabeled SYN545192: batch no. SMU9BP005, 97.0% pure) in 1% aqueous carboxymethylcellulose (CMC) containing 0.1% Tween 80 was administered to 15/sex Han Wistar rats (Charles River (UK) Limited, 7 weeks old, 157-193g for males at 1 mg/kg, 118-145g for females at 1 mg/kg, 195-239g for males at 40 mg/kg, 172-201g for females at 40 mg/kg) in a single oral gavage dose. Groups of three rats/sex were humanely killed at selected times after dosing, blood sample, gastrointestinal tract (and contents) and carcasses were collected or retained. Selected tissues were removed and total radioactivity was determined for each sample. The maximum radioactivity in tissues was detected at 4 hours after dose, with liver and kidney having the highest radioactivity. The radioactivity declined rapidly at 24 hours and further, at 144 hours after dose, the total radioactivity in selected tissues accounted for 2.4% and 2% of total radioactivity administered in males and females dosed with 1 mg/kg, respectively, 1% and <4% of total radioactivity administered in males and females dosed with 40 mg/kg, respectively. The tissue elimination half lives were longer in low dose males than in low dose females. **Supplemental.** (Pan & Leung, 6/27/13)

53206-0005; 270577-SUP; "SYN545192 – The tissue distribution and elimination of [pyrazole-14C]-SYN545192 in the rat following repeated daily oral administration"; (Shaw, J.; Report no. 31050, study No. 190866; 1/13/12); 1 mg/kg [pyrazole-14C]-SYN545192 (Batch no.: 5120PJS001-2, specific activity: 5.55 MBq/mg (150.0 uCi/mg); unlabeled SYN545192: batch no. SMU9BP005, 97.0% pure) in 1% aqueous carboxymethylcellulose (CMC) containing 0.1% Tween 80 was administered to 36 male Han Wistar rats (Charles River (UK) Limited, 7 weeks old, 181-215g) in up to 14 daily oral gavage doses. Groups of three rats were humanely killed at selected times (days 3, 7, 10, 14, as well as 7, 10, 14, 18, 21, 28 and 63 days post dose 14) after dosing, blood sample, gastrointestinal tract (and contents) and carcasses were collected or retained. Selected tissues were removed and total radioactivity was determined for each sample. For 24 hours following daily dosing on days 1 and 14, urine, feces and cage wash was collected from three rats housed temporarily and individually in metabolism cages. The radioactivity following repeated daily oral doses was distributed extensively at 24 hours post dose day 3. The maximum radioactivity in tissues was detected at 24 hours after 14th dose, with liver and kidney having the highest radioactivity. The radioactivity declined following that, at 63 days after dose, the radioactivities in most tissues were close to detection limit. Following the 1st and 14th doses, the major excretion of total radioactivity was via feces. The tissue elimination half lives were calculated. **Supplemental.** (Pan & Leung, 6/28/13)

53206-0005; 270578-SUP; "SYN545192 – Pharmacokinetics of total radioactivity in the rat following intravenous and oral administration of [14-C]-SYN545192"; (Tomlinson, J. and Hutton, E.; Report no. 32748, study No. 194572; 5/11/12); Groups of 4 male and 4 female Han Wistar rats were exposed to a single oral dose of 1 mg or an intravenous injection of 0.25 mg [pyrazole-5-14C]-SYN545192/kg (Batch no.: 5210PJS001-2, specific activity: 5.39 MBq/mg (145.6 uCi/mg); radiochemical purity: 99.5%, unlabeled SYN545192: batch no. SMU9BP005, 97.0% pure), in 1% aqueous carboxymethylcellulose (CMC) containing 0.1% Tween 80 or DMSO:polyethylene glycol (PEG200):saline (10:25:65, v/v/v), respectively. Blood samples were drawn at selected time points over a 4-day period after the oral or i.v. dose, oral bioavailability was determined by comparing the exposures by these two routes. Following single oral dose of 1 mg/kg [14-C]-SYN545192, peak concentrations (C_{max}) of radioactivity in blood for male and female rats (0.172 ug equiv/g and 0.130 ug equiv/g, respectively) were observed at 3.04 hours and 1 hour post dose, respectively. t_{1/2} and AUC_{(0-inf)} for males and females were 47.97 hours, 8.855 ug equiv.h/g and 25.40 hours, 4.742 ug equiv.h/g, respectively. Following single intravenous (bolus) dose of 0.25 mg/kg [14-C]-SYN545192 to male and female rats, C_{0} were 0.072 ug equiv/g and 0.073 ug equiv/g, t_{1/2} and AUC_{(0-inf)} were 53.57 hours and 1.529 ug
equiv.h/g in males, and 30.86 hours and 1.146 ug equiv.h/g in females. The individual bioavailabilities varied in males (111-214%) and females (77-125%), with mean bioavailability of 151% (129% if male #011 was excluded) and 99% in males and females, respectively. This indicated absorption of $[^{14}C]$-SYN545192 was essentially complete. Supplemental. (Pan & Leung, 7/2/13)

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat

53206-0004; 270557; “SYN545192 – Acute Oral Toxicity Study in the Rat (Up and Down Procedure)”; (J. Tavaszi; LAB Research Ltd., H-8200 Veszprem, Szabadsagpuszta, Hungary; Study No. 09/265-001P; 6/8/10); Female Wistar rats were dosed orally with 17.5, 55, or 175 mg/kg of SYN545192 (benzovindiflupyr technical) (batch no. SMU9BP005, purity: 97.0%). The vehicle was aqueous 1% carboxymethylcellulose. The following mortality resulted from the treatment; 17.5 (0/1), 55 (1/4), 175 (3/3). Deaths occurred by day 1 post-dose. Clinical signs included decreased activity, prone position, incoordination, piloerection, dyspnea, decreased respiratory rate, clonic convulsions, and decreased body temperature. No clinical signs were noted for the one animal treated with 17.5 mg/kg. In the necropsy examination, among the animals which died during the observation period, dark red discoloration of the lungs and/or thymus, frothy material in the trachea and enlarged atria of the heart were noted. 55 mg/kg < LD50 (F) < 175 mg/kg; Toxicity Category II; Study acceptable. (Moore, 5/14/13)

53206-0004; 270558; “SYN546039 – Acute Oral Toxicity Study in Rats: Up-and-Down Procedure”; (M. Sieber; Harlan Laboratories Ltd., 4452 Intingen, Switzerland; Study No. D35364; 9/29/11); Female Wistar rats (numbers in parentheses) were dosed orally by gavage with 175 (1), 550 (1) or 2000 (3) mg/kg of SYN546039 (benzovindiflupyr metabolite) (batch no. MES 139/4, purity: 98%). No deaths resulted from the treatment. Clinical signs included decreased activity, prone position, incoordination, piloerection, dyspnea, decreased respiratory rate, clonic convulsions, and decreased body temperature. No clinical signs were noted for the one animal treated with 17.5 mg/kg. The vehicle was aqueous 0.5% carboxymethylcellulose). No deaths resulted from the treatment. Clinical signs included ruffled fur for the 2000 mg/kg animals. No treatment-related lesions were evident in the necropsy examination; LD50 (F) > 2000 mg/kg; Toxicity Category III; Study acceptable. (Moore, 5/15/13)

Acute dermal toxicity

53206-0004, -0068; 270559, 272081; “SYN545192 – Acute Dermal Toxicity Study in the Rat”; (V. Zelenak; LAB Research Ltd., H-8200 Veszprem, Szabadsagpuszta, Hungary; Study No. 09/265-002P; 5/27/10); The skin of five Wistar rats/sex/group was exposed to 2000 mg/kg of SYN545192 (benzovindiflupyr technical) (batch no. SMU9BP005, purity: 97.0%) for 24 hours under a semi-occlusive wrap. Test material was moistened sufficiently with water to ensure good contact with the skin. No deaths resulted from the treatment. No clinical signs were noted. No treatment-related lesions were evident in the necropsy examination. LD50 (M/F) > 2000 mg/kg; Toxicity Category III; Study acceptable, (Moore, 6/24/13)

Acute inhalation toxicity, rat

53206-0004; 270560; “SYN545192 – Acute Inhalation Toxicity Study (Nose-Only) in the Rat”; (K. Nagy; LAB Research Ltd., H-8200 Veszprem, Szabadsagpuszta, Hungary; Study No. 09/265-004P; 5/20/10); Five Wistar rats/sex were exposed nose-only to 0.56 mg/l (gravimetric) of SYN545192 (benzovindiflupyr technical) (batch no. SMU9BP005, purity: 97.0%) for 4 hours. The mean MMAD (GSD) was 3.21 (2.40) um. One female died. Clinical signs included increased, noisy and/or labored respiration, ataxia, lethargy, crouching, clonic convulsions, comatose, cold to the touch, and prone positioning. In the necropsy examination, dark/red discoloration of the lungs was noted for the animal which died. No lesions were evident for
those which survived the observation period. LC50 (M/F) > 0.56 mg/l; Toxicity Category III; Study acceptable. (Moore, 5/15/13)

**Primary eye irritation, rabbit**

53206-0004; 270561; “SYN545192 – Primary Eye Irritation Study in Rabbits”; (M. Mallaun; Harlan Laboratories Ltd., 4414 Fullinsdorf, Switzerland; Study No. D24766; 6/16/11); The eyes of 3 New Zealand White rabbits were treated by ocular instillation with 0.1 g/eye of SYN545192 (benzovindiflupyr technical) (batch no. SMU9BP005; purity: 97.0%). No corneal opacity nor iritis were evident during the 10-day observation period. Conjunctival irritation, grade 1 (3/3) was evident at 24 through 72 hours post-dose, diminishing to grade 1 (1/3) at 7 days and clearing at 10 days. No chemosis was evident during the 10-day observation period. Toxicity Category IV; Study acceptable. (Moore, 5/15/13)

**Primary dermal irritation**

53206-0004; 270562; “SYN545192 – Primary Skin Irritation Study in Rabbits”; (V. Zelenak; LAB Research Ltd., H-8200 Veszprem, Szabadsagpuszta, Hungary; Study No. 09/265-006N; 6/14/10); The skin of 3 New Zealand White rabbits was exposed to 0.5 g/site, one site/animal, of SYN545192 (benzovindiflupyr technical) (batch no. SMU9BP005; purity: 97.0%) for 4 hours under a semi-occlusive wrap. The test material was moistened with 1 ml of water at the time of placement on the skin. Erythema, grade 1 (3/3) was noted at 1 hour post-exposure, diminishing to grade 1 (1/3) at 24 hours and clearing by 48 hours. No edema was noted during the 72-hour observation period. Toxicity Category IV; Study acceptable, (Moore, 6/24/13)

**Dermal sensitization**

53206-0004; 270563; “SYN545192 – Local Lymph Node assay in the Mouse”; (M. Torok-Batho; LAB Research Ltd., H-8200 Veszprem, Szabadsagpuszta, Hungary; Study No. 09/265-037E; 5/19/10); The dorsal skin on the ears of 5 female CBA/J mice/group was treated by topical application with 25 ul/ear/day of 0 (vehicle:acetone:olive oil (4:1)), 5, 10 or 25% preparations of SYN545192 (benzovindiflupyr technical) (batch no. SMU9BP005; purity: 97.0%) for 3 days. A positive control group of 5 animals was treated in the same manner with a 25% preparation of alpha-hexylcinnamaldehyde in acetone:olive oil (4:1). Seventy two hours post-final dose, 20 uCi of ^3^H-thymidine was injected iv into the tail vein of each animal and 5 hours later each animal was euthanized. The draining auricular lymph nodes were removed and single cell suspensions prepared. The cell suspensions were counted using a beta counter and the dpm calculated. A stimulus index (SI) was determined by dividing the mean dpm of each experimental group by the mean value for the vehicle control. An SI value which 3.0 or greater was considered to be a positive response. One of the animals in the 10% treatment group was euthanized in extremis on the 3rd day. Due to the significant toxic effects which were noted for the animals in all of the treatment groups, a 2nd assay was performed in which the ears of 6 animals/group were treated in the same manner with 0.01, 0.1 or 1.0% preparations of the test material in the vehicle. Stimulation indices for all of the treated groups were less than 1.0. The positive control was functional. The test material was not a dermal sensitizer when evaluated in the Localized Lymph Node Assay. Study acceptable. (Moore, 5/16/13)

**SUBCHRONIC STUDIES**  (units of mg/kg/day unless specified)

**Oral toxicity, rat:**

**Rat 4-Week Dietary Toxicity Study**

53206-0040; 270679; “SYN545192 – Twenty-Eight Day Repeated Oral (Dietary) Toxicity Study in the Rat”; (A. Marr; Harlan Laboratories Limited, Shardlow, Derbyshire DE72 2GD, UK;
Study No. 2364/0198; 1/4/10); Five Wistar rats/sex/group received 0, 100, 400 or 1200 ppm of SYN545192 (Benzovindiflupyr technical) (batch no. TE-6341/7; purity not provided) in the diet for 28 days ((M) 0, 9, 36, 107 mg/kg/day, (F) 0, 9, 36, 90 mg/kg/day). No deaths resulted from the treatment. In the evaluation of clinical signs, the only parameter which demonstrated a possible treatment-related effect was foot splay. The foot splay value for females in the 1200 ppm group was greater than that of the control group (p<0.01). The mean body weight gain and mean food consumption of both sexes in the 1200 ppm group were less than the control group values over the course of the study, particularly during the first week of treatment. There was no treatment-related effect upon any of the hematology parameters. Although values for a number of the clinical chemical parameters for the treated animals were statistically different from those of the control group, no apparent treatment-related effect was evident. In the necropsy examination, the mean absolute and relative liver weights of the 1200 ppm males were greater than those of the control group (p<0.01). Centrilobular hypertrophy, minimal, was noted in the livers of the males in the 400 and 1200 ppm groups (0:0/5 vs. 400:2/5, 1200:5/5). In addition, unilateral focal tubular basophilia was evident in the kidneys of all of the treatment group females (0:0/5 vs. 100:1/5, 400:2/5, 1200:3/5). No adverse effect indicated. Rat 4-week dietary toxicity NOEL: (M) 100 ppm (9 mg/kg/day) (based upon the presence of centrilobular hypertrophy in the livers of the 400 ppm males), (F) < 100 ppm (< 9 mg/kg/day) (based upon the incidence of tubular basophilia in the kidneys of the 100 ppm females); Study supplemental. (Moore, 5/24/13)

53206-0048; 270707; “SYN545192 – Investigative 28-Day Rat Dietary Study in Rats with Interim Kills”; (B. Robertson, M. Wood; Charles River, Tranent, Edinburgh, EH33 2NE, UK; Study No. 459287; 8/19/10); Twenty five Wistar rats/sex/group received 0, 100, 750 or 1500 ppm of SYN545192 (benzovindiflupyr technical) (batch no. TE-6341; purity: 98.3%) in the diet for up to 28 days (consumption of a.i. was not calculated for the report). Five animals/sex/group/time point were euthanized on study day 3, 4, 8, 15 and 29. Blood was drawn at those times and stored for analysis of the test material content and/or metabolites. The weights of specified organs were recorded. The mean body weights and food consumption of both sexes in the 750 and 1500 ppm groups were less than those of the control group over the course of the study. The mean relative liver weights of both sexes in the 100 ppm treatment group and above were greater than the control values for the most part throughout the study. No treatment-related lesions were noted in the necropsy examination. No histopathological examination was performed. No adverse effect indicated. No NOEL was established due to cursory nature of the study. Study supplemental. (Moore, 6/25/13)

Rat Subchronic Dietary Toxicity Study

53206-0041; 270685; “SYN545192 – 90 Day Dietary Study in Rats”; (B. Robertson, M. Wood; Charles River, Tranent, Edinburgh, EH33 2NE, UK; Study No. 459292; 9/13/10); Ten Wistar rats/sex/group received 0, 100, 750 or 1500 ppm of SYN545192 (benzovindiflupyr technical) (batch no. TE-6341; purity: 98.3%) in the diet for 90 days ((M) 0, 7.6, 53.8, 108.7 mg/kg/day, (F) 0, 8.2, 58.8, 108.8 mg/kg/day). One male in the 1500 ppm group was found dead on day 78. Death was not apparently related to treatment. The mean body weight gains of both sexes in the 750 and 1500 ppm groups were less than that of the control group over the course of the study (p<0.01). The food consumption for these animals was less than that of the control group. No treatment-related effects were noted for the FOB or motor activity assessments. Evaluation of the hematology parameters did not reveal any treatment-related effects. Although the values for several clinical chemical parameters were statistically different from the control values, any effect was deemed to be related to the failure of the 1500 ppm group animals to thrive as well as the control animals and not a direct effect upon a particular organ (i.e., lower mean serum glucose levels, reduced serum albumin level for the 1500 ppm females). No treatment-related
effect was noted in the urinalysis. The ophthalmological examination did not reveal any treatment-related effect. In the necropsy examination, the relative liver weights of males in the 1500 ppm group were greater than those of the control group (NS). Centrilobular hypertrophy was noted in the liver of both sexes in the 1500 ppm group and the males in the 750 ppm. No adverse effect indicated. Rat Subchronic Dietary Toxicity NOEL: (M/F) 100 ppm ((M) 7.6 mg/kg/day, (F) 8.2 mg/kg/day) (based upon treatment-related effect upon the mean body weight gain of both sexes in the 750 ppm treatment group and incidence of centrilobular hypertrophy in the livers of the 750 ppm males); Study acceptable. (Moore, 5/29/13)

Mouse 4-Week Dietary Toxicity Study
53206-0040; 270684; “SYN545192 – 28 Day Mouse Dietary Toxicity Study”; (J. Shearer, M. Wood; Charles River, Tranent, Edinburgh, EH33 2NE, UK; Study No. 459376; 9/14/10); Five CD-1 mice/sex/group received 0, 100, 300 or 500 ppm of SYN545192 (benzovindiflupyr technical) (batch no. TE-6341; purity: 98.3%) in the diet for 4 weeks ((M) 0, 15.6, 47.8, 81.8 mg/kg/day, (F) 0, 19.0, 57.9, 91.5 mg/kg/day). Another 15 animals/sex/group were treated in the same manner (only seven animals were included in the control group) (Toxicokinetic cohort). On study day 25/26, blood was drawn from the orbital sinus of 3 animals/sex/group/time at hours 2000, 0200, 0800 and 1400 and the presence of the parent compound and 5 metabolites in the plasma was assayed. No deaths resulted from the treatment. The mean body weights and body weight gain of both sexes in the 500 ppm treatment group were less than the control values over the course of the study (p<0.01 or 0.05). There was no apparent treatment-related effect upon the food consumption of these animals. There was no treatment-related effect upon the hematology or clinical chemistry. Although the mean absolute kidney and heart weights of the 500 ppm males were less than the control values (p<0.01 or 0.05), the values were not statistically different when body weight was included as a covariant. In the histological examination, two males and one female in the 500 ppm treatment group demonstrated tubular basophilia in the kidneys. This lesion is indicative of tubulointerstitial nephritis. The parent compound and the five metabolites were present in the plasma at varying concentrations over the course of the sampling period. A dose-related concentration for each of the moieties was apparent. No adverse effect apparent. Mouse Four Week Dietary NOEL: (M/F) 300 ppm ((M) 47.8 mg/kg/day, (F) 57.9 mg/kg/day) (based upon the lower mean body weights and incidence of tubulointerstitial nephritis in the kidneys of both sexes in the 500 mg/kg treatment group); Study supplemental. (Moore, 5/28/13)

Mouse Subchronic Dietary Toxicity Study
53206-0042; 270686; “SYN545192 – 13 Week Dietary Toxicity Study in Mice, Final Report Amendment 1”; (C.J. MacKay, B. Foster; Charles River, Tranent, Edinburgh, EH33 2NE, UK; Study No. 459554; 8/11/11); Ten CD-1 mice/sex/group received 0, 100, 300 or 500 ppm of SYN545192 (benzovindiflupyr technical) (batch no. SMU9BP005; purity: 97%) in the diet for 13 weeks ((M) 0, 17.0, 55.6, 97.9 mg/kg/day, (F) 0, 20.9, 59.6, 102.8 mg/kg/day). An additional 4 animals/sex/group were designated as a satellite cohort from which blood samples were drawn on study day 89 for a toxicokinetic study. Three males in the 500 ppm group were euthanized in extremis on study days 9, 15, and 73. Two of the animals demonstrated apparent treatment-related clinical signs of hunched posture, piloerection and rolling gait. The other animal was suffering from ulcerative dermatitis. The mean body weight gain of both sexes in the 300 and 500 ppm groups was less than that of the control group over the course of the study (NS, p<0.05 or 0.01). The mean food consumption of both sexes in the 500 ppm group was apparently affected during the 1st week of treatment. Thereafter no treatment-related effect on food consumption was noted. There was no treatment-related effect any of the hematology parameters. Although some of the values for the clinical chemical parameters of the treated animals were significantly different from those of the control group, these effects were more
related to the generalized ill health of the treated animals. Likewise in the necropsy examination, the mean absolute weights of numerous organs of the 500 ppm group males were less than the control values. However, no treatment-related effect was apparent when the relative organ weights were compared. In the histological examination, hyperplasia of the mucosa was noted in the colon and rectum of both sexes in the 300 and 500 ppm treatment groups (NS, p<0.05 or 0.001). In addition, an increased incidence of tubular basophilia was noted in the kidneys of the 500 ppm females. No adverse effect indicated. Mouse Subchronic Dietary Toxicity NOEL: (M/F) 100 ppm ((M) 17.0 mg/kg/day, (F) 20.9 mg/kg/dday) (based upon the incidence of mucosal hyperplasia in the colon and rectum of both sexes in the 300 ppm group and the reduced body weight gain of both sexes in the 300 ppm group); Study supplemental (ophthalmology and urinalysis were not included in this study). (Moore, 5/30/13)

Oral toxicity, non-rodent:
Dog Subchronic Oral Toxicity Study
** 53206-0043; 270687; “SYN545192 – 13-Week Oral (Capsule) Toxicity Study in the Beagle Dog”; (D. Pothmann; Harlan Laborabories Ltd., 4452 Itingen, Switzerland; Study No. C41606; 7/7/10); Four beagle dogs/sex/group were dosed orally by capsule with 0, 30, 375 or 750 mg/kg/day of SYN545192 (benzovindiflupyr technical) (batch no. SMU9BP005; purity: 97.0%) for 13 weeks. No deaths resulted from the treatment. Increased incidences of vomiting and loose watery stools were noted for the animals in the 375 and 750 mg/kg groups. Increased salivation was noted for the females in the two higher dose groups as well. Body weight loss was noted for both sexes in the 375 and 750 mg/kg groups during the 1st week of treatment. Reduced body weight gain was evident for these animals over the course of the study. Food consumption was likewise affected for these animals, particularly during the 1st week of the study. There was no treatment-related effect on the hematology, urinalysis or ophthalmological parameters. In the clinical chemistry evaluation, the mean serum triglyceride levels were elevated for both sexes in the 750 mg/kg group at various times during the treatment period (p<0.05). The serum calcium and albumin levels in the males of the 375 and 750 mg/kg groups were less than those of the control group by week 13 of the study (p<0.05). The mean relative liver weights of both sexes in the 750 mg/kg group were greater than those of the control group (NS). In the histopathology examination, increased extramedullary hematopoiesis was noted in the spleens of the males in the 750 mg/kg group (0: 0/4 vs. 750: 4/4, p<0.05). However, the significance of this observation is not apparent because there were no treatment-related effects noted in the hematology parameters. No adverse effect evident. Dog Subchronic Oral Toxicity NOEL: (M/F) 30 mg/kg/day (based upon the lower mean body weight gain and food consumption for both sexes in the 375 mg/kg treatment group); Study acceptable. (Moore, 6/7/13)

Dermal toxicity, 21/28-day or 90-day:
** 53206-0044; 270688; “SYN545192 – 28-Day Dermal Toxicity (Semi-Occlusive) Study in the Wistar Rat, Final Report Amendment 1”; (E.W. Sommer; Harlan Laborabories Ltd., 4452 Itingen, Switzerland; Study No. C72048; 1/16/12); The skin of 10 Wistar rats/sex/group was treated with 0, 100, 300 or 1000 mg/kg/day of SYN545192 (benzovindiflupyr technical) (batch no. SMU9BP005; purity: 97.0%) for 6 hours/day, 5 days/week for 4 weeks. The test material was moistened into a paste with aqueous 0.5% carboxymethyl cellulose. No deaths occurred as a result of the treatment. There were no clinical signs including dermal irritation at the site of application related to the treatment. There was no treatment-related effect upon body weight gain or food consumption. The ophthalmology examination did not reveal any treatment-related lesions. No treatment-related effects were evident in the hematological and clinical chemical evaluations or urinalysis. No treatment-related effect was demonstrated on the absolute or
relative organ weights. The histopathological examination did not reveal any treatment-related lesions. **No adverse effect was indicated.** Rat 28-Day Repeated Dosing Dermal Toxicity NOEL: (M/F) 1000 mg/kg/day (based upon the lack of treatment-related effects at the site of application); **Study acceptable.** (Moore, 6/10/13)

### CHRONIC STUDIES

**Chronic, rat**

** 53206-0050; 270718; “SYN545192 – 104-Week Rat Dietary Carcinogeneity Study with Combined 52-Week Toxicity Study”; (C.J. Mackay; Charles River, Tranent, Edinburgh, EH33 2NE, UK; Study No. 459580; 2/2/12): Fifty two Wistar rats/sex/group (unless otherwise noted) received 0, 25, 100, 400 (females only), or 600 ppm (males only) for 104 weeks in the diet (carcinogenicity cohort) ((M) 0, 1.21, 4.88, 30.2 mg/kg/day, (F) 0, 1.65, 6.66, 27.4 mg/kg/day). An additional chronic toxicity cohort of 12 animals/sex/group received the same treatment levels for 52 weeks ((M) 0, 1.47, 5.76, 34.7 mg/kg/day, (F) 0, 1.90, 7.20, 30.2 mg/kg/day). There was no treatment-related effect on the survival of the study animals. The mean body weight gains of both sexes in the 400/600 ppm treatment groups were less than those of the respective control groups (p<0.01). The mean food consumption of the 400 ppm females was less than that of the control group females over the course of the study. No treatment-related effects were noted in the FOB and motor activity assessment. In the hematology evaluation, the mean hemoglobin concentration, red blood cell count, and hematocrit of the 400 ppm females were less than that of the control group at various times during the study. No significant treatment-related effect was apparent. Similarly, in the clinical chemical evaluation, serum glucose, triglyceride, albumin, globulin and/or urea levels for either sex in the 400/600 ppm treatment group were significantly different from the control values over the course of the study. However, no treatment-related effect was apparent. In the necropsy, the mean relative liver weights of both sexes in the 400/600 treatment group of both the chronic toxicity and carcinogenicity cohorts were greater than those of the treatment group (NS). In the histopathological examination, centrilobular hypertrophy was present in the livers of both sexes in the 400/600 ppm treatment group for both cohorts and in the livers of the males in the 100 ppm treatment group of the carcinogenicity cohort. An increased incidence of eosinophilic cell foci were also noted in the livers of the males in the 600 ppm group of the carcinogenicity cohort. An increased incidence of follicular cell adenomas in the thyroid of the 600 ppm males was noted. **Possible adverse effect: increased incidence of follicular cell adenomas in the thyroid.** **Rat Chronic Dietary Toxicity NOEL:** (M) 25 ppm (1.21 mg/kg/day) (based upon the incidence of centrilobular hypertrophy in the liver of the 100 ppm males in the carcinogenicity cohort); (F) 100 ppm (7.20 mg/kg/day) (based upon centrilobular hypertrophy in the liver of the 400 ppm females in both the chronic toxicity and carcinogenicity cohorts); **Oncogenic potential:** follicular cell adenoma in the thyroid. **Study acceptable.** (Moore, 6/19/13)

**Chronic, dog**

** 53206-0047; 270692; “SYN545192 – 52-Week Oral (Capsule) Toxicity Study in the Beagle Dog”; (L. Braun; Harlan Laboratories Ltd., 4452 Itingen, Switzerland; Study No. C65432; 8/17/11): Four beagle dogs/sex/group were dosed orally by capsule with 0, 25, 250 or 500 mg/kg/day of SYN545192 (benzovindiflupyr technical) (batch no. SMU9BP005; purity: 97.0%) for 52 weeks. No deaths resulted from the treatment. Increased incidences of salivation and vomiting were noted for both sexes in the 250 and 500 mg/kg treatment groups over the course of the study. The mean body weight gains of both sexes in the 500 mg/kg group were less than those of the control group (NS). The mean food consumption values of both sexes in the 250 and 500 mg/kg groups were less than the control values over the course of the study. There
was no treatment-related effect on the hematology, clinical chemistry, urinalysis or ophthalmology. The mean absolute and relative organ weights were not affected by the treatment. The histopathology examination did not reveal any treatment-related lesions. No adverse effect indicated. Dog Chronic Oral Toxicity NOEL: (M/F) 25 mg/kg/day (based upon the increased incidence of salivation and vomiting and lower mean food consumption noted for both sexes in the 250 mg/kg group); Study acceptable. (Moore, 6/13/13)

** Oncogenicity, rat **
See Chronic, rat above.

** Oncogenicity, mouse **
53206-0049; 270717; “SYN545192 – 80-Week Mouse Dietary Carcinogeneity Study”; (C.J. Mackay; Charles River, Tranent, Edinburgh, EH33 2NE, UK; Study No. 459575; 2/6/12); Fifty Crl:CD-1 mice/sex/group received 0, 20, 60 or 200 ppm of SYN545192 (Benzovindiflupyr technical) (batch no. SMU9BP005; purity: 97%) in the diet for 80 weeks ((M) 0, 2.62, 7.55, 26.2 mg/kg/day, (F) 0, 2.89, 8.67, 29.3 mg/kg/day). There was no treatment-related effect on the survival of the study animals. The mean body weight gain and food consumption were not affected over the course of the study. The differential white blood cell count did not reveal any treatment-related effect. The mean absolute and/or relative organ weights were not affected by the treatment. In the histological examination, hyperplasia of the mucosa was noted in the colon and caecum of both sexes in the 200 ppm treatment groups (NS or p< 0.01). The incidence of adenomas in the Harderian gland ranged from 8 to 16% for the males and from 6 to 10% for the females in the treated groups in comparison to 4.0 and 0% for the control males and females, respectively. The historical incidence for these tumors was 5.5 and 2.5% for the males and females, respectively. However the response did not demonstrate a dose-related incidence and there were no non-neoplastic findings that suggested a progression of treatment-related effects leading to tumor formation. The higher incidence was not deemed to be treatment-related. No adverse effect indicated. Mouse Chronic Dietary Toxicity NOEL: 60 ppm ((M): 7.55 mg/kg/day, (F): 8.67 mg/kg/day) (based upon the incidence of mucosal hyperplasia in the colon of both sexes in the 200 ppm treatment group); No oncogenicity was evident. Study acceptable. (Moore, 6/14/13)

GENOTOXICITY

** Gene mutation **
53206-0051; 270720; “SYN545192 – Salmonella Typhimurium and Escherichia Coli Reverse Mutation Assay, Final Report Amendment 1”; (A. Sokolowski; Harlan, Cytotest Cell Research GmbH, 64380 Rossdorf, Germany; Study No. 1244500; 8/29/11); S. typhimurium strains TA98, TA100, TA1535 and TA1537 and E. coli strains WP2 uvrA pKM101 and WP2 pKM101 and were exposed for 48 to 72 hours at 37 °C to SYN545192 (benzovindiflupyr technical) (batch no. SMU9BP005; purity: 97.0%) at concentrations ranging from 3 to 5000 ug/plate with and w/o activation in the first experiment, using plate incorporation as the exposure procedure. In the second experiment, cells were exposed to the same concentrations of the test material with and w/o activation, using the pre-incubation procedure in which cells were exposed to the test material for 60 minutes prior to plating and were incubated for another 48 hours. Each treatment level was plated in triplicate. A phenobarbital and beta-naphthoflavone-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in reverse mutations with or w/o activation. Precipitation of the test material was noted
at concentrations of 1000 ug/plate and above. No adverse effect indicated. The positive controls were functional. Study acceptable. (Moore, 6/27/13)

** 53206-0051; 270722; “SYN545192 – Cell Mutation Assay at the Thymidine Kinase Locus (TK⁺⁻⁻) in Mouse Lymphoma L5178Y Cells”; (H-E. Wollny; Harlan Cytotest Cell Research GmbH, 64380 Rossdorf, Germany; Study No. 1258902; 9/6/10); Mouse lymphoma L5178Y cells were treated with SYN545192 (benzovindiflupyr technical) (batch no. SMU9BP005; purity: 97.0%) at concentrations ranging from 1.3 to 20.0 ug/ml under conditions of non-activation and from 2.5 to 40 ug/ml under conditions of activation for 4 hours at 37°C in the first experiment. In the second experiment, the cells were exposed to concentrations ranging from 2.5 to 60.0 ug/ml under conditions of non-activation and from 10.0 to 60.0 ug/ml under conditions of activation for 4 hours. In the 3rd experiment, cells were exposed to concentrations ranging from 2.5 to 40.0 ug/ml for 4 hours under conditions of non-activation. Duplicate cultures/treatment level were included in the study. A phenobarbital/beta-naphthoflavone-induced rat liver S9 fraction was used to metabolize the test material. Cell survival and viability and mutation frequency for each treatment level were determined and compared to those of the solvent control. There was no dose-related increase in mutation frequency under conditions of either non-activation or activation. Positive controls were functional. No adverse effect indicated. Study acceptable. (Moore, 6/28/13)

** 53206-0051; 270723; “SYN545192 – Chromosome Aberration Test in Human Lymphocytes In Vitro”; (S. Sohnenberger; Harlan Cytotest Cell Research GmbH, 64380 Rossdorf, Germany; Study No. 1258903; 5/17/10); Primary human lymphocyte cultures in whole blood (stimulated with PHA for 70 hours), procured from healthy female volunteers, were treated with SYN545192 (benzovindiflupyr technical) (batch no. SMU9BP005; purity: 97.0%). In trial no. 1, the cells were exposed to concentrations of the test material ranging from 3.1 to 1485 ug/ml with and w/o activation for 4 hours and incubated for an additional 18 hours. In trial no. 2, the non-activated samples were exposed to concentrations of the test material ranging from 0.06 to 30.0 ug/ml for 22 hours. The activated preparations were exposed for 4 hours to concentrations of the test material ranging from 1.3 to 30.0 ug/ml followed by an additional 18 hours of incubation. A phenobarbital/beta-naphthoflavone-induced rat liver S9 fraction was used to metabolize the test material. Two hundred metaphases/treatment level were examined for structural abnormalities. No treatment-related increase in chromosomal aberrations was evident under conditions of nonactivation or activation. The positive controls were functional. No adverse effect indicated. Study acceptable. (Moore, 7/1/13)

** 53206-0051; 270724; “SYN545192 – Micronucleus Test in Bone Marrow Cells of Wistar (Han) Rats, Final Report Amendment 1”; (D.C. Innes, E. Murie, C. Bain; Charles River, Tranent, Edinburgh, EH33 2NE UK; Study No. 786630; 8/23/11); Five male Wistar rats/group were dosed orally by gavage with 0 (vehicle: aqueous 1% carboxymethylcellulose with 0.1% Tween 80), 43.8, 87.5 and 175 mg/kg/day of SYN545192 (benzovindiflupyr technical) (batch no. SMU9BP005; purity: 97.0%) for 2 days (dosing was spaced 24 hours apart). Five females rats/group were dosed in the same manner with 0 or 75 mg/kg/day. These animals were euthanized 24 hours post-final dose. A positive control group of 5 males were dosed orally in the same manner with 50 mg/kg/day of cyclophosphamide and was euthanized at 24 hours post-final dose. The femoral bone marrow was harvested and evaluated for the presence of micronuclei in polychromatic erythrocytes (PCE). Two thousand PCEs/animal were examined and the number of micronucleated PCEs was determined. The ratio of PCE to normochromatic erythrocytes (NCE) was determined by examining 2000 erythrocytes/animal in order to
characterize the possible cytotoxicity. The number of micronucleated-NCEs were also recorded. Treatment-related signs included hunched posture, staggering gait, labored breathing, subdued behavior and piloerection. There was no treatment-related increase in the number of micronuclei per 2000 PCEs. The positive control was functional. No adverse effect indicated. Study acceptable. (Moore, 7/2/13)

REPRODUCTIVE TOXICITY, RAT

** 53206-0046; 270691 834; "SYN545192 – Two-generation reproduction toxicity study in the Han Wistar Rat"; (Adamska, M.; Report no. & study no.C93200, 3/14/12); Groups of 25 male and 25 female Han Wistar rats were exposed to 0, 25, 100 or 600 ppm for males, to 0, 25, 100 or 250 ppm for females, SYN545192 (Batch no. SMU9BP005, 97.0% pure beige powder) in diet for 10 weeks before pairing and during the pairing and after pairing periods in males and during the pairing, gestation, and lactation periods in females for breeding of the F1 litters. Following weaning of the F1 litters on day 21 post partum, F1 animals were selected for the next generation. F1 generation comprised of 25/sex/group was treated with test diets for 10 weeks before pairing and during the pairing and after pairing periods in males and during the pairing, gestation, and lactation periods in females for breeding of the F2 litters. [Parent generation mean test substance intakes: 0, 1.7, 6.8 and 40.5 mg/kg/day in pre-pairing period; 0, 1.2, 4.9 and 29.7 mg/kg/day in after -pairing period for males of 0, 25, 100 or 600 ppm groups, respectively; 0, 2.0, 8.2 and 19.4 mg/kg/day for females in pre-pairing period; 0, 1.9, 7.6 and 17.5 mg/kg/day for females in gestation period; 0, 4.1, 16.8 and 40.2 mg/kg/day for females in lactation period of 0, 25, 100 or 250 ppm groups, respectively]. [F1 generation mean test substance intakes: 0, 1.9, 7.8 and 48.0 mg/kg/day in pre-pairing period; 0, 1.3, 5.2 and 32.5 mg/kg/day in after -pairing period for males of 0, 25, 100 or 600 ppm groups, respectively; 0, 2.1, 8.7 and 22.0 mg/kg/day for females in pre-pairing period; 0, 2.0, 7.9 and 18.3 mg/kg/day for females in gestation period; 0, 4.3, 17.2 and 43.1 mg/kg/day for females in lactation period of 0, 25, 100 or 250 ppm groups, respectively]. P generation Mortality: 1 female rat in 25 ppm group was killed in extremis, 1 female in 250 ppm group died after losing its litter. Statistically significant reduction of food consumption and body weight was observed at pre-pairing period, the after-pairing period in 600ppm group P generation males, and in 250 ppm group P generation females at pre-pairing, gestation and lactation periods. Statistically significant reduction of body weight was observed at 100 ppm group P generation females at pre-pairing, gestation and part of the lactation periods. Statistically significant reduction of cumulative body weight gain was observed in the 250 ppm group P generation females at pre-pairing, gestation and lactation periods, in 100 ppm group P generation females at pre-pairing and lactation periods. Statistically significant increase of liver weight adjusted with body weight in 600 ppm group P males was observed. Statistically significant reduction of male and female F1and F2 pups bodyweights in 250ppm group was observed. Statistically significant reduction of food consumption, body weight and cumulative bodyweight gain at pre-pairing period, after-pairing period in 600 ppm group F1 generation males, and in 250 ppm group F1 generation females at pre-pairing, gestation and lactation periods was observed. Statistically significantly increased liver weight adjusted for body weight in 600 ppm group F1 male pups, in 250 ppm group F1and F2 female pups were observed. Hair loss on left and right forelegs in high dose F1 generation females in pre-pairing, gestation and lactation periods was observed in daily clinical signs or observations. Exophthalmos in left eyes of high dose F1 generation females in gestation and lactation periods was observed in weekly clinical observations. Increased incidence and grade of zona glomerulose hypertrophy in F1 generation 250ppm group females, increased incidence and grade of centrilobular hetatocellular hypertrophy in P and F1 generation 600 ppm group males, increased incidence of patchy fatty changes in liver of F1 males, decreased incidence of hepatocytic glycogen deposits in P and F1 250 ppm group females, increased incidence of...
lactational diestrus in 250 ppm group P and F1 females were observed in microscopic observations. **NOEL (No Observed Effect Level):** Parental and offspring NOEL: 100 ppm due to body weights, food consumption changes, organ weights and microscopic changes in P and F1 generation parent animals and F1 and F2 offspring; Reproduction NOEL: 600ppm for males and 250 ppm for females due to no changes in P and F1 generation fertility and breeding data. **Acceptable.** (Pan & Leung, 7/23/13)

53206-0045; 270690-SUP; "SYN545192 – Dose range-finding reproduction toxicity study in the Han Wistar Rat"; (Whitlow, S.; Report no. & study No.C56928, 12/1/11); Groups of 8 male and female Han Wistar rats (8 weeks old at start of treatment, 254-302 g for males, 7 weeks old at start of treatment, 150-177g for females, from Harlan Laboratories, B. V., Netherland) were exposed to 0, 75, 400 or 600 ppm for males, to 0, 75, 200 or 400 ppm for females, SYN545192 (Batch no. SMU9BP005, 97.0% pure beige powder) in diet for 10 weeks and then were paired for mating. [Mean test substance intakes: 0, 5, 26 and 39 mg/kg/day in pre-pairing period; 0, 4, 20 and 31 mg/kg/day in after -pairing period for males of 0, 75, 400 or 600 ppm groups, respectively; 0, 6, 15, 30 mg/kg/day for females in pre-pairing period; 0, 5, 14 and 29 mg/kg/day for females in gestation period; 0, 13, 31 and 72 mg/kg/day for females in lactation period of 0, 75, 200 or 400 ppm groups, respectively]. All dams and remaining pups were sacrificed on day 21 post partum and males were sacrificed when they were no longer needed for reproduction. Animals were on the test diets for the entire study period (about 17 weeks) including periods of pre-pairing, pairing, gestation and lactation. One male in the 75 ppm group (no. 13) was killed for ethical reasons on day 16 of the pre-pairing period due to wounds in the cervical area and ear, which were not healing. Statistically significant reductions of food consumption was observed in treated males and females at initial pre-pairing period, in treated females during parts of the gestation period, in 200 and 400 ppm group females during parts of the lactation period. Statistically significant reductions of body weight in 400 ppm group females during pre-pairing period, gestation and lactation periods, statistically significant reductions of culmulative body weight gains in 400 ppm group females during pre-pairing period, and gestation periods were observed. Statistically significant increases in total and mean post implantation losses, statistically significant reductions in mean living pups at first litter check and at day 21 post partum in 200 ppm group were considered not related to test substance treatment due to lack of dose response. Statistically significantly increased liver weight adjusted for body weight was observed in 400 and 600 ppm group parent generation males at terminal examinations. Decreased F1 male and female pups weights were observed in the high dose group. The suitable top doses for males and females in 2-generation reproductive toxicity study were determined to be 600 ppm and 250 ppm, respectively. **Supplemental.** (Pan & Leung, 7/9/13)

**DEVELOPMENTAL TOXICITY**

**Rat**

53206-0045; 270689-SUP; "SYN545192 – Dose range-finding prenatal development toxicity study in the Han Wistar Rat"; (Whitlow, S.; Report no. & study No.C73668, 12/1/11); Groups of 10 mated female Han Wistar rats (11 weeks old at day 0 post coitum, 185-229g, from Harlan Laboratories, B. V., Netherland) were exposed to 0, 10, 20 or 30 mg/kg/day SYN545192 (Batch no. SMU9BP005, 97.0% pure beige powder) in 0.5% aqueous carboxymethylcellulose (CMC) from day 6 to day 20 post coitum. All females were sacrificed on day 21 post coitum and fetuses were removed by Caesarean section, both dams and fetuses were examined for maternal or fetal toxicities. No mortality. Test item related clinical signs including uncoordinated movements, circling movements, hunched posture, ruffled fur and decreased activity were observed during
the first week of the treatment period in the 30 mg/kg/day group animals. Statistically significant reductions of food consumption, bodyweight gain in 30 mg/kg/day group, and in 20 mg/kg/day group during part of the treatment period were observed. Statistically significantly increased pre-implantation loss, decreased mean implantation sites and number of total fetuses in 10 mg/kg/day group dams was observed. Statistically significantly decreased mean fetal body weights in 30 mg/kg/day group live fetuses, lower but statistically insignificant reduction of mean fetal body weights in 20 mg/kg/day group live fetuses were observed. No visceral or skeletal abnormalities findings. Based on the results of the preliminary study, dose levels of 0, 7.5, 15 and 30 mg/kg/day were selected for use in the prenatal developmental toxicity study in the rat. **Supplemental.** (Pan & Leung, 7/2/13)

**Rabbit**  
Study not submitted.

### NEUROTOXICITY

**Acute neurotoxicity, rat**  
Study not submitted.

**90-day neurotoxicity, rat**  
53206-0052; 270727; “SYN545192 – 13-Week Dietary Neurotoxicity Study in Rats”; (E.W. Sommer; Harlan Laboratories Ltd., 4452 Ilingen, Switzerland; Study No. C96067; 11/17/11); Twelve male Wistar rats/group received 0, 100, 400 or 800 ppm of SYN545192 (benzovindiflupyr technical) (batch no. SMU9BP005; purity: 97.0%) in the diet for 13 weeks (0, 6.31, 26.0, 50.7 mg/kg/day). Twelve females/group received 0, 100, 250 or 500 ppm of the test material in the diet for the same time period (0, 7.48, 19.2, 38.0 mg/kg/day). No deaths resulted from the treatment. No treatment-related clinical signs were noted in the detailed observations or FOB and motor activity assessments. The mean body weight gains of the 400 and 800 ppm males and the 250 and 500 ppm females were less than those of the control group over the course of the study (NS, p<0.01 or 0.05). The mean food consumption of the 500 ppm females was slightly less than that of the control group over the course of the study (NS). No treatment-related lesions were evident in the ophthalmological examination. The mean relative brain weights of the 400 and 800 ppm males were greater than that of the control group (p<0.05 or 0.01). However, this result was not deemed to be related to any neurotoxic treatment effect. The histological examination of the nervous tissue did not reveal any treatment-related lesions. **No adverse effect indicated.** **Reported Rat Subchronic Dietary NOEL:** (M/F) 100 ppm ((M) 6.31 mg/kg/day, (F) 7.48 mg/kg/day) (based upon the reduced body weight gain demonstrated by the 400 ppm males and the 250 ppm females); **No neurotoxic effect evident.** **Study unacceptable,** possibly upgradeable with the submission of concurrent positive control study data which documents the competency of the staff in performing the required testing protocols. (Moore, 7/3/13)

**Developmental neurotoxicity, rat**  
Study not submitted nor required at this time.

**Delayed neurotoxicity, hen**  
Study not required.
**IMMUNOTOXICITY**

**  53206-0054; 270731; “SYN545192 – A 28-Day Dietary Immunotoxicity Study in CD-1 Female Mice”; (J.M. Wasil; WIL Research Laboratories, LLC. Ashland, OH; Study No. WIL-639155; 2/16/12); Ten CD-1 female mice/group received 0, 100, 200 or 400 ppm of SYN545192 (benzovindiflupyr technical) (batch no. SMU0FP003; purity: 97.7%) in the diet for 28 days (0, 26.4, 47.1, 97.1 mg/kg/day). Another 10 females were dosed by intraperitoneal injection with 50 mg/kg of cyclophosphamide on study days 24 through 27 as the positive control group. On day 24, each animal received an iv injection of 1x10^8 sheep red blood cells (SRBC) (0.2 ml volume). SRBC specific IgM plaques were determined for each animal by incubating a spleen cell suspension preparation with guinea pig complement and SRBC. No deaths occurred during the treatment period. The mean body weight gain of the 400 ppm group was less than that of the control group (p<0.05). There was no apparent treatment-related effect upon food consumption. There were no treatment-related lesions noted in the necropsy examination. There was no treatment-related effect upon the thymus or spleen weights. No treatment-related effect was evident in the plaque-forming cell assay. No adverse effect indicated. The positive control was functional. Study acceptable. (Moore, 7/5/13)

**ENDOCRINE DISRUPTOR STUDIES**

Studies not required at this time.

**SUPPLEMENTAL STUDIES**

**Mechanistic Studies**

53206-0048; 270693; “SYN545192 – 14-Day Rat Dietary Thyroid Mode of Action Study in Rats with 63-Day Recovery Period”; (B. Robertson; Charles River, Tranent, Edinburgh, EH33 2NE, UK; Study No. 521873; 7/13/12); Sixty male Wistar rats/group received 0, 100, 600 or 1200 ppm of SYN545192 (benzovindiflupyr technical) (batch no. SMU9BP005; purity: 97%) in the diet for up to 14 days (0, 9.9, 57.7, 112.8 mg/kg/day). An additional 15 males/group in the control and 1200 ppm treatment groups received the same treatment and then were maintained as a recovery cohort for another 9 weeks. A positive control group of 60 males received 1200 ppm of phenobarbital sodium salt in the diet for up to 14 days. Fifteen animals/group/time point were euthanized on study days 2, 4, 8 and 15. The animals in the recovery cohort were euthanized on study day 78. Two hours prior to their scheduled euthanasia, each animal received a subcutaneous injection of 75 mg/kg of 5-bromo-2'-deoxyuridine (BrdU). At the time of euthanasia, blood was drawn and analyzed for T3, T4 and TSH levels. The liver and thyroid were weighed and examined histologically. Cell proliferation was assessed in the thyroids of each animal by measuring the incorporation of BrdU into the cells during the S-phase of cell division. Enzyme induction in the liver was assessed by measuring microsomal protein in the liver and UDP glucuronosyltransferase activity using thyroxine as a substrate. No deaths resulted from the treatment. The mean body weight gains of the 600 and 1200 ppm treatment groups were less than that of the control group over the 14-day treatment period (p<0.01). The food consumption of the 1200 ppm group was less than that of the control group over the 14-day period. The relative liver weights (based on body weight as a covariance) of the 600 and 1200 ppm groups were greater than that of the control group by the end of the treatment period (p<0.01). The thyroid weights were not affected by the treatment. In the histopathological examination, centrilobular hepatocytic hypertrophy was noted in the livers of the 600 and 1200 ppm treatment groups after 14 days of treatment. No lesions were noted in the thyroids of these
animals. By day 15, the T3 levels in the serum were less than that of the control for all of the treatment groups (p<0.01 or 0.05). The T4 level of the 1200 ppm group was less than that of the control group after 1 and 3 days of treatment. No effect was apparent thereafter. The TSH level for the 1200 ppm group was elevated on day 15, but at no other time point. The microsomal protein content was elevated in the liver for all of the treated groups by day 15 (p <0.01 or 0.05). UDP glucuronosyltransferase activity was elevated in the livers of the 600 and 1200 ppm treatment groups at various time points during the treatment period (based on activity/g of liver) (p<0.01 or 0.05). The percent incorporation of BrdU into thyroid cells during the S-phase of the cell cycle did not demonstrate a consistent dose-related pattern. However, the percent incorporation of BrdU into the thyroid cells of the treated animals was higher than that of the control over the course of the treatment period. All of the assessed parameters had returned to baseline by the end of the 9-week recovery period. Based on these study results, induction of microsomal enzymes in the liver was an apparent consequence of treatment with the test material. There appeared to be a less pronounced cellular proliferative effect in the thyroid of the treated animals. This effect resulted in a minimal reduction in the circulating levels of T3 and T4. These effects correlated well with those demonstrated by the phenobarbital-treated animals. **Rat 14-Day Dietary NOEL:** (M) <100 ppm (<9.9 mg/kg/day) (based upon the increased level of cellular proliferation noted in the thyroids of the 100 ppm animals). Study supplemental. (Moore, 6/21/13)

53206-0048; 270696; “SYN545192 – Effect on Hepatic UDPglucuronosyltransferase Activity towards Thyroxine as Substrate after Dietary Administration for up to 28 Days to Male Rats”; (B.G. Lake; Leatherhead Food Research, Molecular Sciences Department, Leatherhead, Surrey, KT22 7RY, UK; Study No. 5496/1; 2/20/12). Liver samples which had been procured from the rat 28-day dietary toxicity study (study no. 459287, rec. no. 270707) were assayed for microsomal protein and UDP glucuronosyltransferase activity. Liver samples from rats which had been treated with 1200 ppm of phenobarbital in the diet for 7 days were assayed as a positive control. These samples had been procured from another 28-day dietary toxicity study (study no. 521213). The level of microsomal protein in the liver of the treated animals was not appreciably greater than that of the control group after 28 days. There was a treatment-related increase in UDP glucuronosyltransferase activity albeit not necessarily in a dose-related manner. These results indicate that the test material appeared to be an inducer of UDP glucuronosyltransferase activity using thyroxine as a substrate. The positive control was functional. Supplemental Study. (Moore, 6/25/13)

53206-0048; 270700; “SYN545192 – Effect on Rat Thyroid Peroxidase Activity In Vitro”; (B.G. Lake; Leatherhead Food Research, Molecular Sciences Department, Leatherhead, Surrey, KT22 7RY, UK; Study No. 5497/1; 2/6/12); A pooled thyroid microsomal preparation from 5 male Wistar rats was assayed for thyroid peroxidase activity. The preparation was assayed by determining the monoiodination of L-thyroxine as mediated by thyroid peroxidase at concentrations of SYN545192 (benzovindiflupyr technical) (batch no. SMU9BP005; purity: 97.0%) ranging from 0.01 to 10 uM. A positive control, 6-propyl-2-thiouracil (PTU), 10 uM, was also included in the assay. No inhibition of thyroid peroxidase was evident at a 10 uM concentration of the test material. The positive control was functional. The test material apparently does not exert its effect upon the thyroid by inhibiting this enzyme. Study supplemental. (Moore, 6/26/13)

53206-0048; 270703; “SYN545192 – Histological Extension Study of Male Thyroid Tissue from Rat Toxicity Study (Charles River Study No. 459287)”; (B. Robertson; Charles River, Tranent, Edinburgh, EH33 2NE, UK; Study No. 521585; 6/19/12); Thyroid tissue recovered from the study animals in the rat 28-day dietary toxicity study (study no. 459287, rec. no. 270707)
were examined histologically. In this study, twenty five Wistar rats/sex/group received 0, 100, 750 or 1500 ppm of SY5545192 (benzovindiflupyr technical) (batch no. TE-6341; purity: 98.3%) in the diet for up to 28 days. Five animals/sex/group/time point were euthanized on study day 3, 4, 8, 15 and 29. Tissues from animals euthanized at the 4, 8, 15 and 29 day time points were processed, embedded, sectioned, stained with hematoxylin and eosin and examined. Minimal, diffuse, follicular cell hypertrophy was noted in 4 of the thyroid tissue of 20 animals of the 1500 ppm group over the course of the treatment period. The thyroid tissues of two of the 19 males in the 750 ppm group also demonstrated this lesion. No lesion was evident for the 100 ppm treatment group. No adverse effect indicated. Supplemental study. (Moore, 6/26/13)

**STUDIES ON METABOLITES**

** 53206-0051; 270719; “NOA449109 – Salmonella Typhimurium and Escherichia Coli Reverse Mutation Assay”; (A. Sokolowski; Harlan, Cytotest Cell Research GmbH, 64380 Rossdorf, Germany; Study No. 1412200; 8/16/11); S. typhimurium strains TA98, TA100, TA1535 and TA1537 and E. coli strains WP2 uvrA pKM101 and WP2 pKM101 and were exposed for 48 to 72 hours at 37°C to NOA449109 (benzovindiflupyr metabolite) (batch no. AMS 1397/1; purity: 99.5%) at concentrations ranging from 3 to 5000 ug/plate with and w/o activation in the first experiment, using plate incorporation as the exposure procedure. In the second experiment, cells were exposed to concentrations of the test material ranging from 10 to 5000 ug/plate w/o activation and concentrations ranging from 33 to 5000 ug/plate with activation, using the pre-incubation procedure in which cells were exposed to the test material for 60 minutes prior to plating and were incubated for another 48 to 72 hours. Each treatment level was plated in triplicate. A phenobarbital and beta-naphthoflavone-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in reverse mutations with or w/o activation. No adverse effect indicated. The positive controls were functional. Study acceptable. (Moore, 6/27/13)

** 53206-0051; 270721; “SYN546039 – Salmonella Typhimurium and Escherichia Coli Reverse Mutation Assay”; (A. Sokolowski; Harlan, Cytotest Cell Research GmbH, 64380 Rossdorf, Germany; 9/26/11); S. typhimurium strains TA98, TA100, TA1535 and TA1537 and E. coli strains WP2 uvrA pKM101 and WP2 pKM101 and were exposed for 48 to 72 hours at 37°C to SYN546039 (benzovindiflupyr metabolite) (batch no. MES 139/4; purity: 98%) at concentrations ranging from 3 to 5000 ug/plate with and w/o activation in the first experiment, using plate incorporation as the exposure procedure. In the second experiment, cells were exposed to concentrations of the test material ranging from 10 to 5000 ug/plate with and w/o activation, using the pre-incubation procedure in which cells were exposed to the test material for 60 minutes prior to plating and were incubated for another 48 to 72 hours. Each treatment level was plated in triplicate. A phenobarbital and beta-naphthoflavone-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in reverse mutations with or w/o activation. Precipitation of the test material was noted at concentrations of 1000 ug/plate and/or above. No adverse effect indicated. The positive controls were functional. Study acceptable. (Moore, 6/27/13)