Filed on behalf of: Par Pharmaceutical, Inc. et al.

Entered: October 27, 2017

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PAR PHARMACEUTICAL, INC., ARGENTUM PHARMACEUTICAL LLC, AND WEST-WARD PHARMACEUTICALS INTERNATIONAL LIMITED,
Petitioners

v.

NOVARTIS AG
Patent Owner

Case IPR2016-01479[1]
U.S. Patent No. 9,006,224

Before LORA M. GREEN, CHRISTOPHER L. CRUMBLEY, and ROBERT A. POLLOCK, *Administrative Patent Judges*.

PETITIONERS' ORAL ARGUMENT DEMONSTRATIVES

[1] Argentum Pharmaceutical LLC was joined as a party to this proceeding via a Motion for Joinder in IPR2017-01063; West-Ward Pharmaceuticals International Limited was joined as a party via a Motion for Joinder in IPR2017-01078.

Par Pharmaceuticals, Inc., Argentum Pharmaceutical LLC, and West-Ward Pharmaceuticals International Ltd.,

Petitioners

v.

Novartis AG,

Patent Owner

IPR2016-01479, IPR2017-01063, IPR2017-01078

U.S. Patent No. 9,006,224

Oral Argument

November 1, 2017

'224 Patent Claims Methods of Using Everolimus to Treat PNETs

1. A method for treating pancreatic neuroendocrine tumors comprising administering to a human subject in need thereof

a therapeutically effective amount of [everolimus]

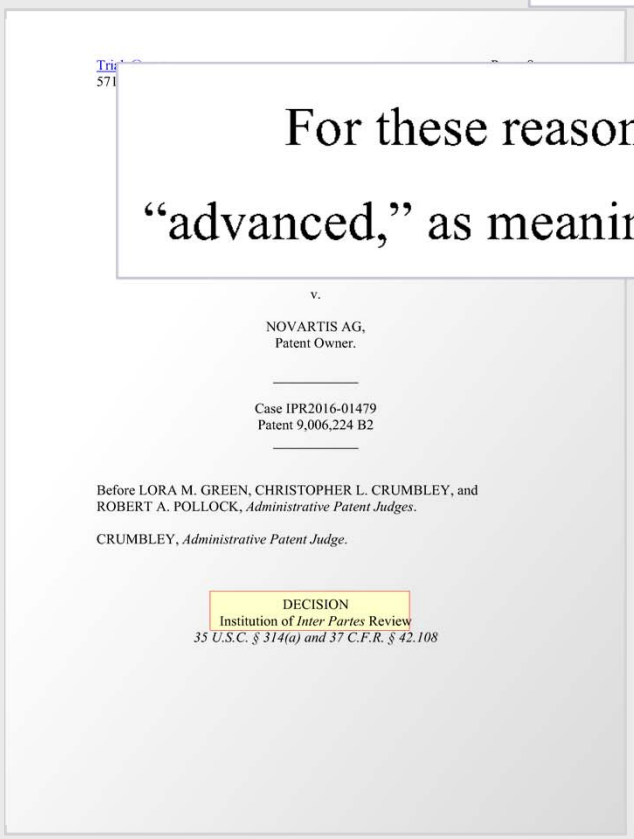
as a monotherapy

and wherein the tumors are advanced tumors

after failure of cytotoxic chemotherapy.

Claim Construction of '224 Patent

DECISION
Institution of *Inter Partes* Review



v.

NOVARTIS AG,
Patent Owner.

Case IPR2016-01479
Patent 9,006,224 B2

Before LORA M. GREEN, CHRISTOPHER L. CRUMBLEY, and ROBERT A. POLLOCK, *Administrative Patent Judges*.

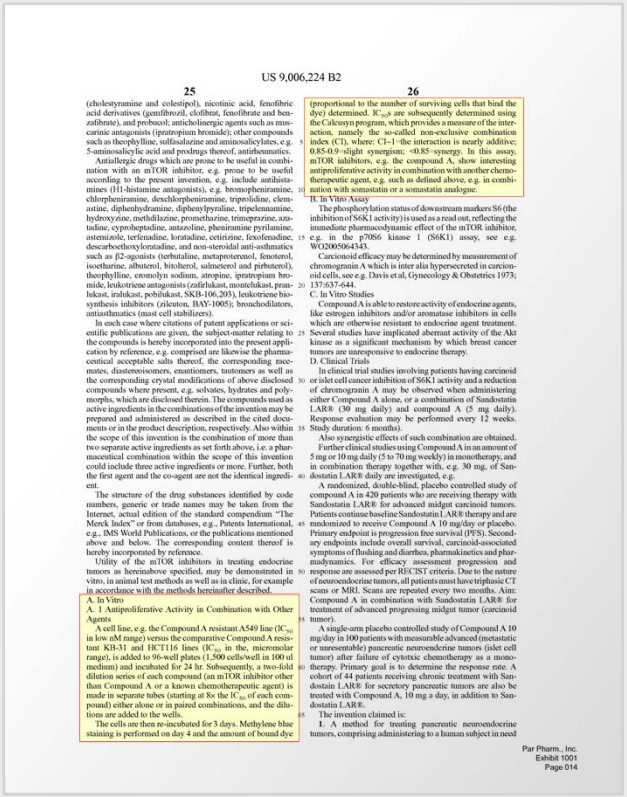
CRUMBLEY, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
35 U.S.C. § 314(a) and 37 C.F.R. § 42.108

For these reasons, we adopt the parties' proposed construction for "advanced," as meaning "metastatic or unresectable."

Inst. Dec. at 7

'224 Patent Specification Examples



US 9,006,224 B2

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(cholestyramine and colestipol), nicotinic acid, fenofibric acid derivatives (gemfibrozil, clofibrat, fenofibrate and benzafibrate), and probucol; anticholinergic agents such as muscarinic antagonists (ipratropium bromide); other compounds such as theophylline, sulfasalazine and aminosalicylates, e.g. 5-aminosalicylic acid and prodrugs thereof, antirheumatics.

Antiallergic drugs which are prone to be useful in combination with an mTOR inhibitor, e.g. prone to be useful according to the present invention, e.g. include antihistamines (H1-histamine antagonists), e.g. bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine, descarboethoxyloratadine, and non-steroidal anti-asthmatics such as β2-agonists (terbutaline, metaproterenol, fenoterol, isoetharine, albuterol, bitolterol, salmeterol and pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (zafirlukast, montelukast, pranlukast, iralukast, pobilukast, SKB-106,203), leukotriene biosynthesis inhibitors (zileuton, BAY-1005); bronchodilators, antiasthmatics (mast cell stabilizers).

In each case where citations of patent applications or scientific publications are given, the subject-matter relating to the compounds is hereby incorporated into the present application by reference, e.g. comprised are likewise the pharmaceutical acceptable salts thereof, the corresponding racemates, diastereoisomers, enantiomers, tautomers as well as the corresponding crystal modifications of above disclosed compounds where present, e.g. solvates, hydrates and polymorphs, which are disclosed therein. The compounds used as active ingredients in the combinations of the invention may be prepared and administered as described in the cited documents or in the product description, respectively. Also within the scope of this invention is the combination of more than two separate active ingredients as set forth above, i.e. a pharmaceutical combination within the scope of this invention could include three active ingredients or more. Further, both the first agent and the co-agent are not the identical ingredient.

The structure of the drug substances identified by code numbers, generic or trade names may be taken from the Internet, actual edition of the standard compendium "The Merck Index" or from databases, e.g., Patents International, e.g., IMS World Publications, or the publications mentioned above and below. The corresponding content thereof is hereby incorporated by reference.

Utility of the mTOR inhibitors in treating endocrine tumors as hereinabove specified, may be demonstrated in vitro, in animal test methods as well as in clinic, for example in accordance with the methods hereinafter described.

A. In Vitro

A. 1 Antiproliferative Activity in Combination with Other Agents

A cell line, e.g. the Compound A resistant A549 line (IC_{50} in low nM range) versus the comparative Compound A resistant KB-31 and HCT116 lines (IC_{50} in the, micromolar range), is added to 96-well plates (1,500 cells/well in 100 ul medium) and incubated for 24 hr. Subsequently, a two-fold dilution series of each compound (an mTOR inhibitor other than Compound A or a known chemotherapeutic agent) is made in separate tubes (starting at 8× the IC_{50} of each compound) either alone or in paired combinations, and the dilutions are added to the wells.

The cells are then re-incubated for 3 days. Methylene blue staining is performed on day 4 and the amount of bound dye

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(proportional to the number of surviving cells that bind the dye) determined. IC_{50}s are subsequently determined using the Calcusyn program, which provides a measure of the interaction, namely the so-called non-exclusive combination index (CI), where: CI~1=the interaction is nearly additive; 0.85-0.9=slight synergism; <0.85=synergy. In this assay, mTOR inhibitors, e.g. the compound A, show interesting antiproliferative activity in combination with another chemotherapeutic agent, e.g. such as defined above, e.g. in combination with somastatin or a somastatin analogue.

B. In Vitro Assay

The phosphorylation status of downstream markers S6 (the inhibition of S6K1 activity) is used as a read out, reflecting the immediate pharmacodynamic effect of the mTOR inhibitor, e.g. in the p70S6 kinase 1 (S6K1) assay, see e.g. WO2005063433.

Carcinoid efficacy may be determined by measurement of chromogranin A which is inter alia hypersecreted in carcinoid cells, see e.g. Davis et al, Gynecology & Obstetrics 1973; 137:637-644.

C. In Vitro Studies

Compound A is able to restore activity of endocrine agents, like estrogen inhibitors and/or aromatase inhibitors in cells which are otherwise resistant to endocrine agent treatment. Several studies have implicated aberrant activity of the Akt kinase as a significant mechanism by which breast cancer tumors are unresponsive to endocrine therapy.

D. Clinical Trials

In clinical trial studies involving patients having carcinoid or islet cell cancer inhibition of S6K1 activity and a reduction of chromogranin A may be observed when administering either Compound A alone, or a combination of Sandostatin LAR® (30 mg daily) and compound A (5 mg daily). Response evaluation may be performed every 12 weeks. Study duration: 6 months).

Also synergistic effects of such combination are obtained.

Further clinical studies using Compound A in an amount of 5 mg or 10 mg daily (5 to 70 mg weekly) in monotherapy, and in combination therapy together with, e.g. 30 mg, of Sandostatin LAR® daily are investigated, e.g.

A randomized, double-blind, placebo controlled study of compound A in 420 patients who are receiving therapy with Sandostatin LAR® for advanced midgut carcinoid tumors. Patients continue baseline Sandostatin LAR® therapy and are randomized to receive Compound A 10 mg/day or placebo. Primary endpoint is progression free survival (PFS). Secondary endpoints include overall survival, carcinoid-associated symptoms of flushing and diarrhea, pharmakinetics and pharmadynamics. For efficacy assessment progression and response are assessed per RECIST criteria. Due to the nature of neuroendocrine tumors, all patients must have triphasic CT scans or MRI. Scans are repeated every two months. Aim: Compound A in combination with Sandostatin LAR® for treatment of advanced progressing midgut tumor (carcinoid tumor).

A single-arm placebo controlled study of Compound A 10 mg/day in 100 patients with measurable advanced (metastatic or unresectable) pancreatic neuroendocrine tumors (islet cell tumor) after failure of cytotxic chemotherapy as a monotherapy. Primary goal is to determine the response rate. A cohort of 44 patients receiving chronic treatment with Sandostatin LAR® for secretory pancreatic tumors are also be treated with Compound A, 10 mg a day, in addition to Sandostatin LAR®.

The invention claimed is:

1. A method for treating pancreatic neuroendocrine tumors, comprising administering to a human subject in need

Par Pharm., Inc.
Exhibit 1001
Page 014

A. In Vitro

A. 1 Antiproliferative Activity in Combination with Other Agents

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Ex. 1001 at 25:54-26:10

Ex. 1001 at 25:54-26:10; Pet. 13; Ex. 1003 at ¶ 33

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