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[Continued on next page]

(54) Title: ABT-263 CRYSTALLINE FORMS AND SOLVATES FOR USE IN TREATING BCL-2 PROTEIN RELATED DISEASES

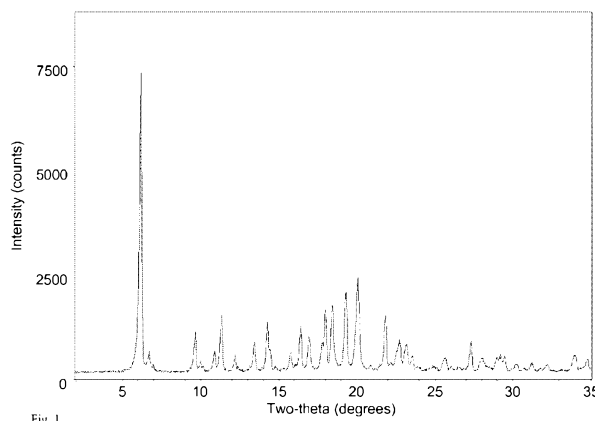
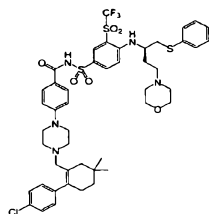


Fig. 1



(57) Abstract: ABT-263 free base and crystalline forms thereof are suitable active pharmaceutical ingredients for pharmaceutical compositions useful in treatment of a disease characterized by overexpression of one or more anti-apoptotic Bcl-2 family proteins, for example cancer.

WO 2011/034934 A1

**WO 2011/034934 A1**



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This application claims priority benefit of U.S. provisional application Serial No. 61/244,051 filed on September 20, 2009.

Cross-reference is made to the following pending U.S. applications containing subject matter related to the present application: Serial No. 12/770,112 titled "Lipid formulation of apoptosis promoter"; Serial No. 12/770,174 titled "Stabilized lipid formulation of apoptosis promoter"; Serial No. 12/770,205 titled "Solid oral formulation of ABT-263"; and Serial No. 12/770,299 titled "Formulation for oral administration of apoptosis promoter", all filed on April 29, 2010.

The entire disclosure of each of the above applications is incorporated herein by reference.

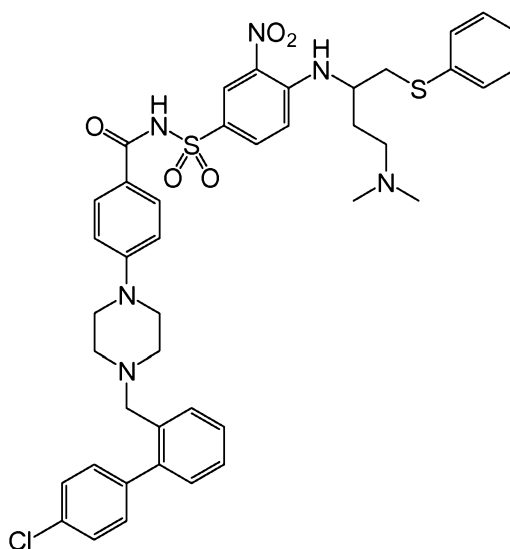
#### FIELD OF THE INVENTION

The present invention relates to the apoptosis-promoting agent ABT-263, to solid state forms thereof and formulations containing and/or prepared with such solid state forms, and to methods of use thereof for treating diseases characterized by overexpression of anti-apoptotic Bcl-2 family proteins. More particularly the invention relates to crystalline forms of ABT-263 useful, for example, as active pharmaceutical ingredient (API) in preparing pharmaceutical compositions for administration of ABT-263 to a subject in need thereof.

#### BACKGROUND OF THE INVENTION

Evasion of apoptosis is a hallmark of cancer (Hanahan & Weinberg (2000) Cell 100:57–70). Cancer cells must overcome a continual bombardment by cellular stresses such as DNA damage, oncogene activation, aberrant cell cycle progression and harsh microenvironments that would cause normal cells to undergo apoptosis. One of the primary means by which cancer cells evade apoptosis is by up-regulation of anti-apoptotic proteins of the Bcl-2 family.

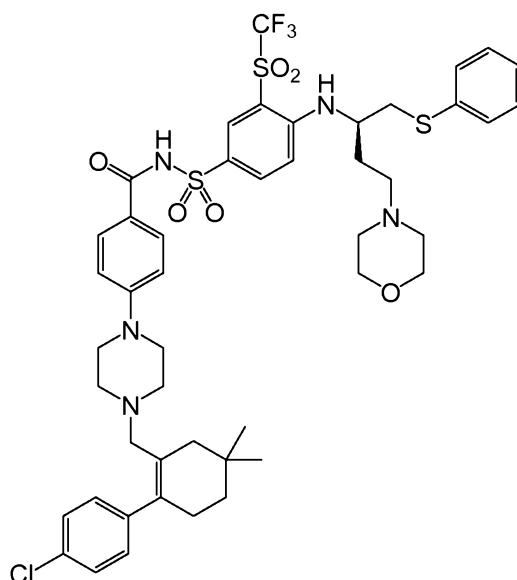
Compounds that occupy the BH3 binding groove of Bcl-2 proteins have been described, for example by Bruncko *et al.* (2007) J. Med. Chem. 50:641–662. These compounds have included N-(4-(4-((4'-chloro-(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzene-sulfonamide, otherwise known as ABT-737, which has the formula:



ABT-737 binds with high affinity (<1 nM) to proteins of the Bcl-2 family (specifically Bcl-2, Bcl-X<sub>L</sub> and Bcl-w). It exhibits single-agent activity against small-cell lung cancer (SCLC) and lymphoid malignancies, and potentiates pro-apoptotic effects of other chemotherapeutic agents. ABT-737 and related compounds, and methods to make such compounds, are disclosed in U.S. Patent Application Publication No. 2007/0072860 of Bruncko *et al.*

More recently, a further series of compounds has been identified having high binding affinity to Bcl-2 family proteins. These compounds, and methods to make them, are disclosed in U.S. Patent Application Publication No. 2007/0027135 of Bruncko *et al.* (herein “the ’135 publication”), incorporated by reference herein in its entirety, and can be seen from their formula to be structurally related to ABT-737.

One compound, identified as “Example 1” in the ’135 publication, is N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide, otherwise known as ABT-263. This compound has a molecular weight of 974.6 g/mol and has the formula:



Tse *et al.* (2008) Cancer Res. 68:3421–3428 and supplementary data thereto available at Cancer Research Online ([cancerres.aacrjournals.org/](http://cancerres.aacrjournals.org/)) have reported animal pharmacokinetic studies of ABT-263, synthesized as described in the '135 publication. The drug was formulated in solution in 10% dimethyl sulfoxide (DMSO) in polyethylene glycol (PEG) 400 or in 10% ethanol / 30% PEG400 / 60% Phosal 50-PG™.

A particular type of disease for which improved therapies are needed is non-Hodgkin's lymphoma (NHL). NHL is the sixth most prevalent type of new cancer in the U.S. and occurs primarily in patients 60–70 years of age. NHL is not a single disease but a family of related diseases, which are classified on the basis of several characteristics including clinical attributes and histology.

One method of classification places different histological subtypes into two major categories based on natural history of the disease, *i.e.*, whether the disease is indolent or aggressive. In general, indolent subtypes grow slowly and are generally incurable, whereas aggressive subtypes grow rapidly and are potentially curable. Follicular lymphomas are the most common indolent subtype, and diffuse large-cell lymphomas constitute the most common aggressive subtype. The oncoprotein Bcl-2 was originally described in non-Hodgkin's B-cell lymphoma.

Treatment of follicular lymphoma typically consists of biologically-based or combination chemotherapy. Combination therapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) is routinely used, as is combination therapy with rituximab, cyclophosphamide, vincristine and prednisone (RCVP). Single-agent therapy with rituximab (targeting CD20, a phosphoprotein uniformly expressed on the

surface of B-cells) or fludarabine is also used. Addition of rituximab to chemotherapy regimens can provide improved response rate and increased progression-free survival.

Radioimmunotherapy agents, high-dose chemotherapy and stem cell transplants can be used to treat refractory or relapsed non-Hodgkin's lymphoma. Currently, there is not an approved treatment regimen that produces a cure, and current guidelines recommend that patients be treated in the context of a clinical trial, even in a first-line setting.

First-line treatment of patients with aggressive large B-cell lymphoma typically consists of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), or dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R).

Most lymphomas respond initially to any one of these therapies, but tumors typically recur and eventually become refractory. As the number of regimens patients receive increases, the more chemotherapy-resistant the disease becomes. Average response to first-line therapy is approximately 75%, 60% to second-line, 50% to third-line, and about 35–40% to fourth-line therapy. Response rates approaching 20% with a single agent in a multiple relapsed setting are considered positive and warrant further study.

Current chemotherapeutic agents elicit their antitumor response by inducing apoptosis through a variety of mechanisms. However, many tumors ultimately become resistant to these agents. Bcl-2 and Bcl-X<sub>L</sub> have been shown to confer chemotherapy resistance in short-term survival assays *in vitro* and, more recently, *in vivo*. This suggests that if improved therapies aimed at suppressing the function of Bcl-2 and Bcl-X<sub>L</sub> can be developed, such chemotherapy-resistance could be successfully overcome.

#### SUMMARY OF THE INVENTION

The compound ABT-263, when prepared according to Example 1 of the '135 publication, is recovered as an amorphous, glassy solid that is not well suited as active pharmaceutical ingredient (API) for downstream formulation. More particularly, this amorphous form of ABT-263 is difficult and therefore expensive to purify and presents process control problems. One approach, exemplified in copending U.S. provisional application Serial No. 61/174,274 filed on April 30, 2009 (incorporated by reference herein without admission that it constitutes prior art to the present invention), is to prepare ABT-263 as a crystalline salt. In another approach, the present inventors have now been able to prepare a series of novel crystalline forms of ABT-263 free base suitable for use as API in a wide variety of formulation types, including those where the API is present in particulate form

together with excipients, for example in orally deliverable tablets or capsules.

In one embodiment, the invention provides the compound N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)-benzenesulfonamide free base in a solid crystalline Form I, characterized at least by a powder X-ray diffraction peak at any one or more of the following positions: 6.21, 6.72, 12.17, 18.03 and 20.10° 2 $\theta$ ,  $\pm$  0.2° 2 $\theta$ .

In one embodiment, the invention provides the compound N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)-benzenesulfonamide free base in a solid crystalline Form II, characterized at least by a powder X-ray diffraction peak at any one or more of the following positions: 5.79, 8.60, 12.76, 15.00 and 20.56° 2 $\theta$ ,  $\pm$  0.2° 2 $\theta$ .

In one embodiment, the invention provides the compound N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)-benzenesulfonamide free base in a solid crystalline form, wherein the crystalline form is a solvate comprising the compound solvated with an organic solvent.

In one embodiment, the invention provides use of the compound of the invention and one or more pharmaceutically acceptable excipients in the manufacture of a medicament comprising a therapeutically effective amount of the compound of the invention for the treatment of a neoplastic disease selected from the group consisting of cancer, mesothelioma, bladder cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, bone cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal and/or duodenal) cancer, chronic lymphocytic leukemia, acute lymphocytic leukemia, esophageal cancer, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, hepatocellular (hepatic and/or biliary duct cancer, primary or secondary central nervous system tumor, primary or secondary brain tumor, Hodgkin's disease,



chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphoma, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, multiple myeloma, oral cancer, non-small-cell lung cancer, prostate cancer, small-cell lung cancer, cancer of the kidney and/or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system, primary central nervous system lymphoma, non-Hodgkin's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, cancer of the spleen, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma and combinations thereof.

In one embodiment, the invention provides use of the compound of the invention in the manufacture of a medicament for the treatment of a neoplastic disease, wherein said manufacture comprises dissolving the compound of the invention in a pharmaceutically acceptable solvent or mixture of solvents, and wherein said neoplastic disease selected from the group consisting of cancer, mesothelioma, bladder cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, breast cancer, uterine rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal and/or duodenal) cancer, chronic lymphocytic leukemia, acute lymphocytic leukemia, esophageal cancer, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, hepatocellular (hepatic and/or biliary duct) cancer, primary or secondary central nervous system tumor, primary or secondary brain tumor, Hodgkin's disease, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphoma lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, multiple myeloma, oral cancer, non-small-cell lung cancer, prostate cancer, small-cell lung cancer, cancer of the kidney and/or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system, primary central nervous system lymphoma, non-Hodgkin's lymphoma, spinal axis tumors, brain stem cancer of the spleen, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma and combinations thereof.

In one embodiment, the invention provides a method for the treatment of a neoplastic disease selected from the group consisting of cancer, mesothelioma, bladder cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or

intraocular melanoma, ovarian cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, bone cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal and/or duodenal) cancer, chronic lymphocytic leukemia, acute lymphocytic leukemia, esophageal cancer, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, hepatocellular (hepatic and/or biliary duct cancer, primary or secondary central nervous system tumor, primary or secondary brain tumor, Hodgkin's disease, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphoma, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, multiple myeloma, oral cancer, non-small-cell lung cancer, prostate cancer, small-cell lung cancer, cancer of the kidney and/or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system, primary central nervous system lymphoma, non-Hodgkin's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, cancer of the spleen, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma and combinations thereof, the method comprising administering to a subject in need thereof a therapeutically effective amount of a medicament comprising a compound according to the invention or of a pharmaceutical composition of the invention.

In one embodiment, the invention provides N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide (ABT-263) free base in solid crystalline form.

In a further embodiment, the invention provides a solvent-free crystal polymorph of ABT-263 free base characterized herein and designated Form I ABT-263 free base.

In a still further embodiment, the invention provides a solvent-free crystal polymorph of ABT-263 free base characterized herein and designated Form II ABT-263 free base.

In a variety of still further embodiments, the invention provides solvated crystal forms of ABT-263 free base with organic solvents.

In a still further embodiment, the invention provides a pharmaceutical composition comprising crystalline ABT-263 free base (for example Form I or Form II as provided above) and one or more pharmaceutically acceptable excipients.

In a still further embodiment, the invention provides a process for preparing a pharmaceutical solution composition of ABT-263 comprising dissolving crystalline ABT-263 free base (for example Form I or Form II as provided above) in a pharmaceutically acceptable solvent or mixture of solvents.

In a still further embodiment, the invention provides a method for treating a disease characterized by apoptotic dysfunction and/or overexpression of an anti-apoptotic Bcl-2 family protein, comprising administering to a subject having the disease a therapeutically effective amount of ABT-263 free base in crystalline form (for example Form I or Form II as provided above) or a pharmaceutical composition comprising ABT-263 free base in crystalline form (for example Form I or Form II as provided above) and one or more pharmaceutically acceptable excipients. Examples of such a disease include many neoplastic diseases including cancers. A specific illustrative type of cancer that can be treated according to the present method is non-Hodgkin's lymphoma. Another specific illustrative type of cancer that can be treated according to the present method is chronic lymphocytic leukemia. Yet another specific illustrative type of cancer that can be treated according to the present method is acute lymphocytic leukemia, for example in a pediatric patient.

There is still further provided a method for maintaining in bloodstream of a human cancer patient, for example a patient having non-Hodgkin's lymphoma, a therapeutically effective plasma concentration of ABT-263 and/or one or more metabolites thereof, comprising administering to the subject a pharmaceutical composition comprising ABT-263

free base in crystalline form (for example Form I or Form II as provided above) and one or more pharmaceutically acceptable excipients, in a dosage amount of about 50 to about 1000 mg ABT-263 per day, at an average dosage interval of about 3 hours to about 7 days.

Additional embodiments of the invention, including more particular aspects of those provided above, will be found in, or will be evident from, the detailed description that follows.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a PXRD scan of solvent-free crystal polymorph Form I ABT-263 free base.

Fig. 2 is a PXRD scan of solvent-free crystal polymorph Form II ABT-263 free base.

#### DETAILED DESCRIPTION

The term “free base” is used for convenience herein to refer to ABT-263 parent compound as distinct from any salt thereof, while recognizing that the parent compound is, strictly speaking, zwitterionic and thus does not always behave as a true base.

The term “solvent-free” herein refers to crystal lattice of a polymorph such as Form I or Form II ABT-263 free base, from which solvent has been removed by desolvation. Solvent can be present in small amounts in solid-state particles of the compound without being part of or otherwise affecting the crystal structure of the polymorph; such presence of solvent is still consistent with the polymorph being “solvent-free” as the term is used herein.

ABT-263 free base can be prepared by a process as described in Example 1 of above-cited U.S. Patent Application Publication No. 2007/0027135, the entire disclosure of which is incorporated by reference herein. The product of this process is an amorphous, glassy solid. A powder can be prepared from this product, for example by freeze-drying or precipitation techniques.

Solvates of ABT-263 free base have been prepared as described below. The starting product can be any solid-state form of ABT-263 free base, including the amorphous form prepared according to the '135 publication.

A measured amount of ABT-263 free base (as indicated, any solid-state form can be used) was suspended in each of a number of solvents or solvent mixtures as indicated in Table 1. The resulting suspensions were agitated at ambient temperature, while protected from light. After a period of time sufficient to permit solvation of ABT-263 free base in each case, crystals were harvested by filter centrifugation. The resulting solvates were characterized by powder X-ray diffraction (PXRD).

**Table 1. Preparation of ABT-263 free base crystalline solvates**

Solvent	Weight of compound (mg)	Volume of solvent (ml)
2-Propanol	106.2	1.0
1-Propanol	160.1	1.25
Ethyl acetate:Ethanol (1:3, v/v)	108.7	0.5
Methyl acetate:Hexanes (1:1, v/v)	76.2	0.5
Chloroform	110.3	0.5
Methanol	107.3	1.0
1,4-Dioxane:Hexanes (1:2, v/v)	99.5	0.75
Toluene	104.3	1.0
Benzene	100.3	0.5
Ethyl acetate	~250	0.25
Isopropyl acetate	~250	0.25
Methyl acetate	~250	0.25
Trifluorotoluene	~250	0.25

PXRD data were collected using a G3000 diffractometer (Inel Corp., Artenay, France) equipped with a curved position-sensitive detector and parallel-beam optics. The diffractometer was operated with a copper anode tube (1.5 kW fine focus) at 40 kV and 30 mA. An incident-beam germanium monochromator provided monochromatic radiation. The diffractometer was calibrated using the attenuated direct beam at one-degree intervals. Calibration was checked using a silicon powder line position reference standard (NIST 640c). The instrument was computer-controlled using Symphonix software (Inel Corp., Artenay, France) and the data were analyzed using Jade software (version 6.5, Materials Data, Inc., Livermore, CA). The sample was loaded onto an aluminum sample holder and leveled with a glass slide.

PXRD peaks for individual solvates determined as above are listed in Tables 2–14. Peak positions are typically  $\pm 0.2$  degrees two-theta ( $^{\circ} 2\theta$ ).

**Table 2. PXRD peak listing: ABT-263 free base 1-propanol solvate**

Peak Position ( $^{\circ} 2\theta$ )
4.88
6.72
8.79
9.62
12.19
12.53
13.46
13.71

Peak Position (° 2θ)
14.51
15.32
16.10
17.59
18.20
19.30
19.64
20.38
20.91
23.30

**Table 3. PXRD peak listing: ABT-263 free base 2-propanol solvate**

Peak Position (° 2θ)
4.88
6.76
8.78
9.64
12.15
12.49
13.41
13.73
15.30
16.10
16.35
17.51
18.26
19.34
19.60
20.33
23.35

**Table 4. PXRD peak listing: ABT-263 free base benzene solvate**

Peak Position (° 2θ)
4.28
4.60
7.75
8.54
10.88
11.16
12.49
12.97
15.48
18.10
18.42
18.75

Peak Position (° 2 $\theta$ )
19.53
20.19
20.59
21.25

**Table 5. PXRD peak listing: ABT-263 free base chloroform solvate**

Peak Position (° 2 $\theta$ )
4.99
9.61
13.39
13.85
15.85
16.05
16.68
17.60
18.51
19.25
19.67
20.10
21.37
23.39
23.78
24.48

**Table 6. PXRD peak listing: ABT-263 free base 1,4-dioxane/hexanes solvate**

Peak Position (° 2 $\theta$ )
4.85
8.81
9.61
9.94
12.17
12.49
13.39
13.66
15.30
16.20
17.60
18.24
19.27
19.55

**Table 7. PXRD peak listing: ABT-263 free base methyl acetate/hexanes solvate**

Peak Position (° 2 $\theta$ )
5.66
7.29

Peak Position (° 2θ)
9.31
9.70
10.38
11.34
12.56
12.93
14.58
14.88
15.83
17.18
17.71
17.99
18.24
18.63
19.46
20.79
21.16
21.46

**Table 8. PXRD peak listing: ABT-263 free base methanol solvate**

Peak Position (° 2θ)
5.03
5.25
5.66
8.88
9.66
10.05
12.53
13.67
13.89
15.52
18.54
18.93
19.36
19.96
20.33

**Table 9. PXRD peak listing: ABT-263 free base toluene solvate**

Peak Position (° 2θ)
4.48
7.61
8.92
10.85
12.35
12.75



Peak Position (° 2θ)
13.34
14.73
15.23
16.47
18.33
18.89
19.28
19.92
20.29
21.41
22.31
23.66
24.36

**Table 10. PXRD peak listing: ABT-263 free base ethanol/ethyl acetate solvate**

Peak Position (° 2θ)
5.03
6.82
8.89
9.68
9.97
12.41
12.65
13.80
14.65
15.60
16.26
17.87
18.52
19.43
19.94

**Table 11. PXRD peak listing: ABT-263 free base ethyl acetate solvate**

Peak Position (° 2θ)
5.66
7.32
9.31
9.64
11.36
12.56
14.61
14.85
18.03
18.31
18.58

19.56
20.70
21.07

**Table 12. PXRD peak listing: ABT-263 free base isopropyl acetate solvate**

<b>Peak Position (° 2θ)</b>
5.64
7.36
9.50
11.45
12.52
14.72
15.14
16.89
18.08
18.45
19.55
20.49
20.89
21.23

**Table 13. PXRD peak listing: ABT-263 free base methyl acetate solvate**

<b>Peak Position (° 2θ)</b>
5.63
7.24
9.27
9.66
11.27
12.53
14.51
14.77
15.78
16.10
16.44
17.64
17.92
18.15
18.52
19.39
20.70

**Table 14. PXRD peak listing: ABT-263 free base trifluorotoluene solvate**

<b>Peak Position (° 2θ)</b>
4.49
4.99
9.78

Peak Position ( $^{\circ}$ 2 $\theta$ )
12.35
12.73
13.94
15.51
15.80
17.81
18.52
19.56
19.99
20.35
21.00
21.60

In addition, single crystals of anisole, pyridine and 2-propanol solvates were prepared for crystallographic analysis by the following method. Single crystals were individually mounted on MiTeGen polyimide mounts. Intensity data were collected on a Bruker D8 system equipped with an APEX II CCD camera. Data were collected at 100 K with graphite-monochromated Mo K $\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ). Data were collected in four sets using  $\omega$ - $\phi$  scans with  $\omega$  steps of  $0.5^{\circ}$  and  $\phi$  steps of  $90^{\circ}$ . The data were collected with 20 s frame exposures. Data were processed using APEX2 software. Corrections for Lorentz polarization effects were applied. Absorption was negligible. All structures were solved using direct methods that yielded the non-hydrogen atoms. All presented hydrogen atoms were located in Fourier-difference electron density maps. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms associated with carbon atoms were refined in geometrically constrained riding positions. Hydrogen atoms associated with oxygen atoms were included in the located positions. Refinement was achieved with the use of SHELXTL crystallographic software.

To prepare single crystals of an anisole solvate, amorphous ABT-263 free base was dissolved in 0.5 ml anisole. Single crystals were observed two days later. Crystallographic data for the anisole solvate are presented in Table 15, and PXRD peaks calculated from crystal structure are listed in Table 16.

**Table 15. Crystallographic information for ABT-263 free base anisole solvate**

Lattice Type	Orthorhombic
Space Group	P212121
Cell Length a	12.112 $\text{\AA}$
Cell Length b	14.120 $\text{\AA}$
Cell Length c	38.710 $\text{\AA}$
Cell Angle $\alpha$	$90.0^{\circ}$

Cell Angle $\beta$	90.0°
Cell Angle $\gamma$	90.0°
Cell Volume	6620.24 Å <sup>3</sup>
Z	4

**Table 16. PXRD peak listing: ABT-263 free base anisole solvate  
(calculated from crystal structure)**

<b>Peak Position (° 2<math>\theta</math>)</b>
4.56
7.74
8.60
9.62
10.64
11.08
11.81
12.53
12.74
14.68
16.08
17.18
17.34
18.71
19.42
19.84
20.37
20.74

To prepare single crystals of a pyridine solvate, crystalline ABT-263 free base (900 mg) was suspended in a pyridine/hexanes mixture (8 ml, 1:4 v/v). The suspension was allowed to settle and the supernatant was removed and heated to 50°C. Amorphous ABT-263 free base (100 mg) was dissolved in the supernatant at 50°C and the resulting solution was cooled to room temperature. Single crystals were observed one week later and were found to be a pyridine solvate. Crystallographic data for the pyridine solvate are presented in Table 17, and PXRD peaks calculated from crystal structure are listed in Table 18.

**Table 17. Crystallographic information for ABT-263 free base pyridine solvate**

Lattice Type	Monoclinic
Space Group	P21
Cell Length a	13.901 Å
Cell Length b	11.931 Å
Cell Length c	38.935 Å
Cell Angle $\alpha$	90.0°
Cell Angle $\beta$	90.154°
Cell Angle $\gamma$	90.0°
Cell Volume	6457.46 Å <sup>3</sup>
Z	4

**Table 18. PXRD peak listing: ABT-263 free base pyridine solvate  
(calculated from crystal structure)**

Peak Position (° 2 $\theta$ )
4.54
6.75
7.75
8.68
9.76
10.06
11.72
11.91
12.72
14.74
16.32
16.79
17.33
17.55
18.70
19.28
19.72

To prepare single crystals of a 2-propanol solvate, approximately 100 mg ABT-263 free base was dissolved in approximately 1 g ethyl acetate. The resulting solution was added to 2.7 g 2-propanol. Crystalline seeds of ABT-263 free base Form I were added. Single crystals were observed two days later. Crystallographic data for the 2-propanol solvate are presented in Table 19, and PXRD peaks calculated from crystal structure are listed in Table 20.

**Table 19. Crystallographic information for ABT-263 free base 2-propanol solvate**

Lattice Type	Monoclinic
Space Group	P21

Cell Length a	13.834 Å
Cell Length b	36.105 Å
Cell Length c	19.104 Å
Cell Angle $\alpha$	90.0°
Cell Angle $\beta$	110.56°
Cell Angle $\gamma$	90.0°
Cell Volume	8934.19 Å <sup>3</sup>
Z	6

**Table 20. PXRD peak listing: ABT-263 free base 2-propanol solvate**  
(calculated from crystal structure)

Peak Position (° 2 $\theta$ )
4.94
6.82
8.84
9.84
12.30
12.78
13.66
13.92
15.52
16.24
16.58
17.74
18.54
19.52
19.86
20.21
23.55

Comparison with Table 3 shows close correspondence between peak positions calculated from single crystal data and those determined by PXRD. Minor shifts in some peaks may reflect different temperature conditions in the two methods (100 K for single crystals; room temperature for PXRD).

The suspension crystallization technique described above is only one of several known ways to generate the supersaturation necessary to prepare solvated crystals. Other procedures include:

- anti-solvent addition (ABT-263 is dissolved in a first solvent or mixture of solvents wherein it is soluble at high concentration, and an anti-solvent that is miscible with the first solvent or mixture of solvents is added to the resulting solution);

- variants of the above anti-solvent addition procedure, for example where the solution of ABT-263 is added to the anti-solvent;
- temperature gradient (ABT-263 is dissolved in a solvent or mixture of solvents at elevated temperature, and the resulting solution is cooled to lower temperatures, *e.g.*, sub-ambient temperatures);
- solvent evaporation (ABT-263 is dissolved in a solvent or mixture of solvents, which is then evaporated); and
- reactive crystallization (ABT-263 in a form of a salt with an acid is dissolved in a solvent or mixture of solvents, and the resulting solution is added to a solution of a neutralizing agent such as sodium hydroxide, sodium carbonate or sodium bicarbonate, causing the free base to crystallize out; alternatively an ABT-263 salt with a base can be used, in which case pH is adjusted with an acidic neutralizing agent to cause the free base to crystallize out).

Combinations of the above procedures can be used if desired. Specific details such as rate of generating supersaturation (for example by rate of addition of anti-solvent or neutralizing agent, rate of cooling or rate of solvent evaporation) can readily be optimized by one of ordinary skill in the art without undue experimentation.

Desolvation of the ethanol/ethyl acetate solvate, for example by air-drying, provides a solvent-free crystalline form of ABT-263 free base. This crystalline form is designated Form I. A PXRD scan of Form I ABT-263 free base is shown in Fig. 1. PXRD peaks for Form I ABT-263 free base are listed in Table 21. A PXRD pattern having peaks substantially as indicated therein can be used to identify crystalline ABT-263 free base, more particularly Form I ABT-263 free base. The phrase “substantially as indicated” in the present context means having peaks that are not shifted more than about  $0.2^\circ 2\theta$  from the indicated position.

**Table 21. PXRD peak listing: solvent-free crystal polymorph Form I ABT-263 free base**

Peak Position ( $^\circ 2\theta$ )
6.21
6.72
9.66
10.92
11.34
12.17
14.28
16.40
16.95
17.81

Peak Position (° 2 $\theta$ )
18.03
18.47
19.32
20.10
21.87

Desolvation of most solvates, including 1-propanol, 2-propanol, methanol, dioxane/hexanes, methyl acetate/hexanes, ethyl acetate, methyl acetate, isopropyl acetate and chloroform solvates, provides a solvent-free crystalline form of ABT-263 free base that is shown by PXRD to be identical to the crystalline form produced by desolvation of the ethanol/ethyl acetate solvate.

Desolvation of the pyridine, anisole and trifluorotoluene solvates provides a solvent-free crystalline form of ABT-263 free base that is shown by PXRD to be different from the form produced by desolvation of the ethanol/ethyl acetate solvate. The crystalline form derived from desolvation of the pyridine, anisole or trifluorotoluene solvate is designated Form II. A PXRD scan of Form II ABT-263 free base is shown in Fig. 2. PXRD peaks for Form II ABT-263 free base are listed in Table 22. A PXRD pattern having peaks substantially as indicated therein can be used to identify crystalline ABT-263 free base, more particularly Form II ABT-263 free base.

**Table 22. PXRD peak listing: solvent-free crystal polymorph Form II ABT-263 free base**

Peak Position (° 2 $\theta$ )
5.79
8.60
9.34
10.79
11.36
11.59
12.76
13.23
13.73
14.01
14.72
15.00
16.28
17.07
17.48
18.75
19.34



Peak Position (° 2 $\theta$ )
19.71
20.56
21.35

Desolvation of benzene and toluene solvates has been observed on different occasions to provide crystals identified as Form I or Form II. When a higher crystallinity product is achieved, it most closely matches Form II.

PXRD peaks especially diagnostic for Form I ABT-263 free base, in particular for distinguishing Form I from Form II, include the peaks at 6.21, 6.72, 12.17, 18.03 and 20.10° 2 $\theta$ , in each case  $\pm 0.2^\circ$  2 $\theta$ . In one embodiment, Form I ABT-263 free base is characterized at least by a peak at any one or more of these positions. In another embodiment, Form I ABT-263 free base is characterized at least by a peak at each of these positions. In yet another embodiment, Form I ABT-263 free base is characterized by a peak at each of the positions shown in Table 21.

PXRD peaks especially diagnostic for Form II ABT-263 free base, in particular for distinguishing Form II from Form I, include the peaks at 5.79, 8.60, 12.76, 15.00 and 20.56° 2 $\theta$ , in each case  $\pm 0.2^\circ$  2 $\theta$ . In one embodiment, Form II ABT-263 free base is characterized at least by a peak at any one or more of these positions. In another embodiment, Form II ABT-263 free base is characterized at least by a peak at each of these positions. In yet another embodiment, Form II ABT-263 free base is characterized by a peak at each of the positions shown in Table 22.

Any of the crystalline forms of ABT-263 free base, including solvated forms, can be useful as API for preparation of pharmaceutical compositions. However, solvent-free forms such as Form I and Form II are generally preferred for this purpose.

Solvated forms are, as indicated above, useful as process intermediates in preparation of solvent-free forms such as Form I and Form II. It will therefore be clear from the disclosure herein that an embodiment of the present invention provides ABT-263 free base in a crystalline form solvated with an organic solvent. The term "an organic solvent" will be understood herein to embrace single organic solvents and mixtures of organic solvents. More particularly according to this embodiment there is provided a crystalline ABT-263 free base solvate selected from the group consisting of 1-propanol, 2-propanol, methanol, benzene, toluene, dioxane/hexanes, methyl acetate/hexanes, ethanol/ethyl acetate, ethyl acetate, methyl acetate, isopropyl acetate, chloroform, pyridine, anisole and trifluorotoluene solvates.

It will further be clear from the disclosure herein that an embodiment of the present

invention provides a process for preparing Form I ABT-263 free base, comprising desolvating an ABT-263 free base solvate selected from the group consisting of 1-propanol, 2-propanol, methanol, dioxane/hexanes, methyl acetate/hexanes, ethanol/ethyl acetate, ethyl acetate, methyl acetate, isopropyl acetate and chloroform solvates.

It will still further be clear from the disclosure herein that an embodiment of the present invention provides a process for preparing Form II ABT-263 free base, comprising desolvating an ABT-263 free base solvate selected from the group consisting of pyridine, anisole and trifluorotoluene solvates. In a related embodiment, a process for preparing Form II ABT-263 free base comprises desolvating an ABT-263 free base solvate selected from the group consisting of benzene and toluene solvates.

ABT-263 crystalline free base, for example Form I, Form II or a combination thereof, can be used in preparation of pharmaceutical compositions suitable for any route of administration, including oral, to a subject in need thereof. Thus in some embodiments of the present invention, a pharmaceutical composition is provided, comprising ABT-263 crystalline free base and one or more pharmaceutically acceptable excipients. Such compositions can be prepared by any known process of pharmacy. In one embodiment, the composition comprises crystalline Form I ABT-263 free base. In another embodiment, the composition comprises crystalline Form II ABT-263 free base. According to any of these embodiments, the composition can be deliverable, for example, by the oral route. Other routes of administration include without limitation parenteral, sublingual, buccal, intranasal, pulmonary, topical, transdermal, intradermal, ocular, otic, rectal, vaginal, intragastric, intracranial, intrasynovial and intra-articular routes.

Where it is desired to provide ABT-263 free base in solution form, for example in a liquid formulation for oral or parenteral administration, the ABT-263 free base will not, of course, be present in such a formulation in crystalline form; indeed, the presence of crystals is generally undesired in such a formulation. However, crystalline ABT-263 free base of the present invention can nonetheless be important as API in a process for preparing such a formulation. Thus the invention further provides a process for preparing a pharmaceutical solution composition of ABT-263 comprising dissolving crystalline ABT-263 free base in a pharmaceutically acceptable solvent or mixture of solvents. In one embodiment, the process comprises dissolving crystalline Form I ABT-263 free base in a solvent or mixture of solvents. In another embodiment, the composition comprises dissolving crystalline Form II ABT-263 free base in a solvent or mixture of solvents.

Even where the desired formulation is one containing ABT-263 free base in amorphous

form, for example a solid melt formulation, crystalline ABT-263 free base can still be useful as API in a process for preparing such a formulation. For example, an illustrative process for preparing a solid dispersion of ABT-263 free base comprises

- (a) dissolving an API comprising (i) crystalline ABT-263 free base, (ii) a pharmaceutically acceptable water-soluble polymeric carrier and (iii) a pharmaceutically acceptable surfactant in a suitable solvent; and
- (b) removing the solvent to provide a solid matrix comprising the polymeric carrier and the surfactant and having the ABT-263 free base dispersed in an essentially non-crystalline form therein.

Another illustrative process comprises adding crystalline ABT-263 free base to at least one pharmaceutically acceptable polymer and at least one solubilizer; preparing a homogeneous melt from the resulting mixture; and allowing the melt to solidify to obtain a solid dispersion product.

As API, a crystalline form of ABT-263 free base such as Form I, Form II or mixtures thereof has advantages over the amorphous form hitherto available. For example, purification of API to the high degree of purity required by most regulatory authorities is more efficient and therefore costs less where the API is in crystalline as opposed to amorphous form. Physical and chemical stability, and therefore shelf-life of the API solid, is also typically better for crystalline than amorphous forms. Ease of handling is improved over the amorphous form, which tends to be oily or sticky. Drying is more straightforward and more easily controlled in the case of the crystalline material, which has a well-defined drying or desolvation temperature, than in the case of the amorphous material, which has greater affinity for organic solvents and no well-defined drying temperature. Particle size distribution can be controlled more readily in crystalline material, for example by manipulation of the crystallization process. Downstream processing using crystalline API permits enhanced process control. In preparing a liquid formulation, for example a solution in a lipid carrier, crystalline ABT-263 dissolves faster and has less tendency to form a gel during dissolution. These advantages are illustrative and non-limiting.

Pharmaceutical compositions comprising crystalline ABT-263 free base, or prepared using crystalline ABT-263 free base as API, contain ABT-263 in an amount that can be therapeutically effective when the composition is administered to a subject in need thereof according to an appropriate regimen. Dosage amounts are expressed herein as free base equivalent amounts unless the context requires otherwise. Typically, a unit dose (the amount

administered at a single time), which can be administered at an appropriate frequency, *e.g.*, twice daily to once weekly, is about 10 to about 1,000 mg. Where frequency of administration is once daily (q.d.), unit dose and daily dose are the same. Illustratively, the unit dose of ABT-263 in a composition of the invention can be about 25 to about 1,000 mg, more typically about 50 to about 500 mg, for example about 50, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450 or about 500 mg. Where the composition is prepared as a discrete dosage form such as a tablet or capsule, a unit dose can be deliverable in a single dosage form or a small plurality of dosage forms, most typically 1 to about 10 dosage forms.

The higher the unit dose, the more desirable it becomes to select excipients that permit a relatively high loading of API (in this case ABT-263 free base) in the formulation. Typically, the concentration of ABT-263 free base in a formulation prepared according to the invention is at least about 1%, *e.g.*, about 1% to about 25%, by weight, but lower and higher concentrations can be acceptable or achievable in specific cases. Illustratively, the ABT-263 free base equivalent concentration in various embodiments is at least about 2%, *e.g.*, about 2% to about 20%, by weight, for example about 5%, about 10% or about 15%, by weight of the formulation.

A composition prepared according to the invention comprises, in addition to the API, one or more pharmaceutically acceptable excipients. If the composition is to be prepared in solid form for oral administration, for example as a tablet or capsule, it typically includes at least one or more solid diluents and one or more solid disintegrants. Optionally, the excipients further include one or more binding agents, wetting agents and/or antifrictional agents (lubricants, anti-adherents and/or glidants). Many excipients have two or more functions in a pharmaceutical composition. Characterization herein of a particular excipient as having a certain function, *e.g.*, diluent, disintegrant, binding agent, *etc.*, should not be read as limiting to that function. Further information on excipients can be found in standard reference works such as Handbook of Pharmaceutical Excipients, 3rd ed. (Kibbe, ed. (2000), Washington: American Pharmaceutical Association).

Suitable diluents illustratively include, either individually or in combination, lactose, including anhydrous lactose and lactose monohydrate; lactitol; maltitol; mannitol; sorbitol; xylitol; dextrose and dextrose monohydrate; fructose; sucrose and sucrose-based diluents such as compressible sugar, confectioner's sugar and sugar spheres; maltose; inositol; hydrolyzed cereal solids; starches (*e.g.*, corn starch, wheat starch, rice starch, potato starch, tapioca starch, *etc.*), starch components such as amylose and dextrates, and modified or

processed starches such as pregelatinized starch; dextrins; celluloses including powdered cellulose, microcrystalline cellulose, silicified microcrystalline cellulose, food grade sources of  $\alpha$ - and amorphous cellulose and powdered cellulose, and cellulose acetate; calcium salts including calcium carbonate, tribasic calcium phosphate, dibasic calcium phosphate dihydrate, monobasic calcium sulfate monohydrate, calcium sulfate and granular calcium lactate trihydrate; magnesium carbonate; magnesium oxide; bentonite; kaolin; sodium chloride; and the like. Such diluents, if present, typically constitute in total about 5% to about 95%, for example about 20% to about 90%, or about 50% to about 85%, by weight of the composition. The diluent or diluents selected preferably exhibit suitable flow properties and, where tablets are desired, compressibility.

Microcrystalline cellulose and silicified microcrystalline cellulose are particularly useful diluents, and are optionally used in combination with a water-soluble diluent such as mannitol. Illustratively, a suitable weight ratio of microcrystalline cellulose or silicified microcrystalline cellulose to mannitol is about 10:1 to about 1:1, but ratios outside this range can be useful in particular circumstances.

Suitable disintegrants include, either individually or in combination, starches including pregelatinized starch and sodium starch glycolate; clays; magnesium aluminum silicate; cellulose-based disintegrants such as powdered cellulose, microcrystalline cellulose, methylcellulose, low-substituted hydroxypropylcellulose, carmellose, carmellose calcium, carmellose sodium and croscarmellose sodium; alginates; povidone; crospovidone; polacrillin potassium; gums such as agar, guar, locust bean, karaya, pectin and tragacanth gums; colloidal silicon dioxide; and the like. One or more disintegrants, if present, typically constitute in total about 0.2% to about 30%, for example about 0.5% to about 20%, or about 1% to about 10%, by weight of the composition.

Sodium starch glycolate is a particularly useful disintegrant, and typically constitutes in total about 1% to about 20%, for example about 2% to about 15%, or about 5% to about 10%, by weight of the composition.

Binding agents or adhesives are useful excipients, particularly where the composition is in the form of a tablet. Such binding agents and adhesives should impart sufficient cohesion to the blend being tableted to allow for normal processing operations such as sizing, lubrication, compression and packaging, but still allow the tablet to disintegrate and the composition to be absorbed upon ingestion. Suitable binding agents and adhesives include, either individually or in combination, acacia; tragacanth; glucose; polydextrose; starch including pregelatinized starch; gelatin; modified celluloses including methylcellulose,

carmellose sodium, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose, hydroxyethylcellulose and ethylcellulose; dextrans including maltodextrin; zein; alginic acid and salts of alginic acid, for example sodium alginate; magnesium aluminum silicate; bentonite; polyethylene glycol (PEG); polyethylene oxide; guar gum; polysaccharide acids; polyvinylpyrrolidone (povidone or PVP), for example povidone K-15, K-30 and K-29/32; polyacrylic acids (carbomers); polymethacrylates; and the like. One or more binding agents and/or adhesives, if present, typically constitute in total about 0.5% to about 25%, for example about 1% to about 15%, or about 1.5% to about 10%, by weight of the composition.

Povidone and hydroxypropylcellulose, either individually or in combination, are particularly useful binding agents for tablet formulations, and, if present, typically constitute about 0.5% to about 15%, for example about 1% to about 10%, or about 2% to about 8%, by weight of the composition.

Wetting agents, if present, are normally selected to maintain the drug in close association with water, a condition that can improve bioavailability of the composition. Non-limiting examples of surfactants that can be used as wetting agents include, either individually or in combination, quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride; dioctyl sodium sulfosuccinate; polyoxyethylene alkylphenyl ethers, for example nonoxynol 9, nonoxynol 10 and octoxynol 9; poloxamers (polyoxyethylene and polyoxypropylene block copolymers); polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides, polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, for example ceteth-10, laureth-4, laureth-23, oleth-2, oleth-10, oleth-20, steareth-2, steareth-10, steareth-20, steareth-100 and polyoxyethylene (20) cetostearyl ether; polyoxyethylene fatty acid esters, for example polyoxyethylene (20) stearate, polyoxyethylene (40) stearate and polyoxyethylene (100) stearate; sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate; polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80; propylene glycol fatty acid esters, for example propylene glycol laurate; sodium lauryl sulfate; fatty acids and salts thereof, for example oleic acid, sodium oleate and triethanolamine oleate; glyceryl fatty acid esters, for example glyceryl monooleate, glyceryl monostearate and glyceryl palmitostearate; tyloxapol; and the like. One or more wetting agents, if present, typically constitute in total about 0.1% to about 15%, for example about 0.2% to about 10%, or about 0.5% to about 7%, by weight of the composition.

Nonionic surfactants, more particularly poloxamers, are examples of wetting agents that

can be useful herein. Illustratively, a poloxamer such as Pluronic™ F127, if present, can constitute about 0.1% to about 10%, for example about 0.2% to about 7%, or about 0.5% to about 5%, by weight of the composition.

Lubricants reduce friction between a tableting mixture and tableting equipment during compression of tablet formulations. Suitable lubricants include, either individually or in combination, glyceryl behenate; stearic acid and salts thereof, including magnesium, calcium and sodium stearates; hydrogenated vegetable oils; glyceryl palmitostearate; talc; waxes; sodium benzoate; sodium acetate; sodium fumarate; sodium stearyl fumarate; PEGs (*e.g.*, PEG 4000 and PEG 6000); poloxamers; polyvinyl alcohol; sodium oleate; sodium lauryl sulfate; magnesium lauryl sulfate; and the like. One or more lubricants, if present, typically constitute in total about 0.05% to about 10%, for example about 0.1% to about 5%, or about 0.2% to about 2%, by weight of the composition. Sodium stearyl fumarate is a particularly useful lubricant.

Anti-adherents reduce sticking of a tablet formulation to equipment surfaces. Suitable anti-adherents include, either individually or in combination, talc, colloidal silicon dioxide, starch, DL-leucine, sodium lauryl sulfate and metallic stearates. One or more anti-adherents, if present, typically constitute in total about 0.05% to about 10%, for example about 0.1% to about 7%, or about 0.2% to about 5%, by weight of the composition. Colloidal silicon dioxide is a particularly useful anti-adherent.

Glidants improve flow properties and reduce static in a tableting mixture. Suitable glidants include, either individually or in combination, colloidal silicon dioxide, starch, powdered cellulose, sodium lauryl sulfate, magnesium trisilicate and metallic stearates. One or more glidants, if present, typically constitute in total about 0.05% to about 10%, for example about 0.1% to about 7%, or about 0.2% to about 5%, by weight of the composition. Colloidal silicon dioxide is a particularly useful glidant.

Other excipients such as buffering agents, stabilizers, antioxidants, antimicrobials, colorants, flavors and sweeteners are known in the pharmaceutical art and can be used in compositions of the present invention. Tablets can be uncoated or can comprise a core that is coated, for example with a nonfunctional film or a release-modifying or enteric coating. Capsules can have hard or soft shells comprising, for example, gelatin (in the form of hard gelatin capsules or soft elastic gelatin capsules), starch, carrageenan and/or HPMC, optionally together with one or more plasticizers.

A solid orally deliverable composition of the present invention is not limited by any process used to prepare it. Any suitable process of pharmacy can be used, including dry

blending with or without direct compression, and wet or dry granulation.

If the composition is to be prepared in liquid (including encapsulated liquid) form, the API (crystalline ABT-263 free base) can be, for example, dissolved in a suitable carrier, typically one comprising a lipid solvent for the API. The higher the unit dose, the more desirable it becomes to select a carrier that permits a relatively high concentration of the drug in solution therein. Typically, the free base equivalent concentration of API in the carrier is at least about 10 mg/ml, *e.g.*, about 10 to about 500 mg/ml, but lower and higher concentrations can be acceptable or achievable in specific cases. Illustratively, the drug concentration in various embodiments is at least about 10 mg/ml, *e.g.*, about 10 to about 250 mg/ml, or at least about 20 mg/ml, *e.g.*, about 20 to about 200 mg/ml, for example about 20, about 25, about 30, about 40, about 50, about 75, about 100 or about 150 mg/ml.

The carrier can be substantially non-aqueous, *i.e.*, having no water, or having an amount of water that is small enough to be, in practical terms, essentially non-deleterious to performance or properties of the composition. Typically, the carrier comprises zero to less than about 5% by weight water. It will be understood that certain ingredients useful herein can bind small amounts of water on or within their molecules or supramolecular structures; such bound water if present does not affect the “substantially non-aqueous” character of a carrier as defined herein.

In some embodiments, the carrier comprises one or more glyceride materials. Suitable glyceride materials include, without limitation, medium to long chain mono-, di- and triglycerides. The term “medium chain” herein refers to hydrocarbyl chains individually having no less than about 6 and less than about 12 carbon atoms, including for example C<sub>8</sub> to C<sub>10</sub> chains. Thus glyceride materials comprising caprylyl and capryl chains, *e.g.*, caprylic/capric mono-, di- and/or triglycerides, are examples of “medium chain” glyceride materials herein. The term “long chain” herein refers to hydrocarbyl chains individually having at least about 12, for example about 12 to about 18, carbon atoms, including for example lauryl, myristyl, cetyl, stearyl, oleyl, linoleyl and linolenyl chains. Medium to long chain hydrocarbyl groups in the glyceride materials can be saturated, mono- or polyunsaturated.

In one embodiment the carrier comprises a medium chain and/or a long chain triglyceride material. A suitable example of a medium chain triglyceride material is a caprylic/capric triglyceride product such as, for example, Captex 355 EP™ of Abitec Corp. and products substantially equivalent thereto. Suitable examples of long chain triglycerides include any pharmaceutically acceptable vegetable oil, for example canola, coconut, corn,



cottonseed, flaxseed, olive, palm, peanut, safflower, sesame, soy and sunflower oils, and mixtures of such oils. Oils of animal, particularly marine animal, origin can also be used, including for example fish oil.

A carrier system that has been found particularly useful comprises two essential components: a phospholipid, and a pharmaceutically acceptable solubilizing agent for the phospholipid. It will be understood that reference in the singular to a (or the) phospholipid, solubilizing agent or other formulation ingredient herein includes the plural; thus combinations, for example mixtures, of more than one phospholipid, or more than one solubilizing agent, are expressly contemplated herein. The solubilizing agent, or the combination of solubilizing agent and phospholipid, also solubilizes the drug, although other carrier ingredients, such as a surfactant or an alcohol such as ethanol, optionally present in the carrier can in some circumstances provide enhanced solubilization of the drug.

Any pharmaceutically acceptable phospholipid or mixture of phospholipids can be used. In general such phospholipids are phosphoric acid esters that yield on hydrolysis phosphoric acid, fatty acid(s), an alcohol and a nitrogenous base. Pharmaceutically acceptable phospholipids can include without limitation phosphatidylcholines, phosphatidylserines and phosphatidylethanolamines. In one embodiment the composition comprises phosphatidylcholine, derived for example from natural lecithin. Any source of lecithin can be used, including animal sources such as egg yolk, but plant sources are generally preferred. Soy is a particularly rich source of lecithin that can provide phosphatidylcholine for use in the present invention.

Illustratively, a suitable amount of phospholipid is about 15% to about 75%, for example about 30% to about 60%, by weight of the carrier, although greater and lesser amounts can be useful in particular situations.

Ingredients useful as components of the solubilizing agent are not particularly limited and will depend to some extent on the desired concentration of drug and of phospholipid. In one embodiment, the solubilizing agent comprises one or more glycols, one or more glycolides and/or one or more glyceride materials.

Glycols are generally suitable only for non-encapsulated formulations or where a soft capsule shell is to be used, and tend to be incompatible with hard shells such as hard gelatin shells. Suitable glycols include propylene glycol and polyethylene glycols (PEGs) having molecular weight of about 200 to about 1,000 g/mol, *e.g.*, PEG-400, which has an average molecular weight of about 400 g/mol. Such glycols can provide relatively high solubility of the drug; however the potential for oxidative degradation of ABT-263 can be increased when

in solution in a carrier comprising such glycols, for example because of the tendency of glycols to produce superoxides, peroxides and/or free hydroxyl radicals. The higher the glycol content of the carrier, the greater may be the tendency for degradation of the ABT-263. In one embodiment, therefore, one or more glycols are present in a total glycol amount of at least about 1% but less than about 50%, for example less than about 30%, less than about 20%, less than about 15% or less than about 10% by weight of the carrier. In another embodiment, the carrier comprises substantially no glycol.

Glycolides are glycols such as propylene glycol or PEG esterified with one or more organic acids, for example medium- to long-chain fatty acids. Suitable examples include propylene glycol monocaprylate, propylene glycol monolaurate and propylene glycol dilaurate products such as, for example, Capmul PG-8™, Capmul PG-12™ and Capmul PG-2L™ respectively of Abitec Corp. and products substantially equivalent thereto.

Suitable glyceride materials for use together with a phospholipid include, without limitation, those mentioned above. Where one or more glyceride materials are present as a major component of the solubilizing agent, a suitable total amount of glycerides is an amount effective to solubilize the phospholipid and, in combination with other components of the carrier, effective to maintain the drug and antioxidant in solution. For example, glyceride materials such as medium chain and/or long chain triglycerides can be present in a total glyceride amount of about 5% to about 70%, for example about 15% to about 60% or about 25% to about 50%, by weight of the carrier.

Additional solubilizing agents that are other than glycols, glycolides or glyceride materials can be included if desired. Such agents, for example N-substituted amide solvents such as dimethylformamide (DMF) and N,N-dimethylacetamide (DMA), can, in specific cases, assist in raising the limit of solubility of the drug in the carrier, thereby permitting increased drug loading. However, the carriers useful herein generally provide adequate solubility of ABT-263 without such additional agents.

Even when a sufficient amount of a glycol, glycolide or glyceride material is present to solubilize the phospholipid, the resulting carrier solution and/or the drug-carrier system may be rather viscous and difficult or inconvenient to handle. In such cases it may be found desirable to include in the carrier a viscosity reducing agent in an amount effective to provide acceptably low viscosity. An example of such an agent is an alcohol, more particularly ethanol, which is preferably introduced in a form that is substantially free of water, for example 99% ethanol, dehydrated alcohol USP or absolute ethanol. Excessively high concentrations of ethanol should, however, generally be avoided. This is particularly true

where, for example, the drug-carrier system is to be administered in a gelatin capsule, because of the tendency of high ethanol concentrations to result in mechanical failure of the capsule. In general, suitable amounts of ethanol are 0% to about 25%, for example about 1% to about 20% or about 3% to about 15%, by weight of the carrier. Glycols such as propylene glycol or PEG and medium-chain mono- and diglycerides (for example caprylic/capric mono- and diglycerides) can also be helpful to lower viscosity; where the drug-carrier system is to be encapsulated in a hard capsule such as a hard gelatin capsule, medium-chain mono- and diglycerides are particularly useful in this regard.

Optionally, the carrier further comprises a pharmaceutically acceptable non-phospholipid surfactant. One of skill in the art will be able to select a suitable surfactant for use in a composition of the invention. Illustratively, a surfactant such as polysorbate 80 can be included in an amount of 0% to about 5%, for example 0% to about 2% or 0% to about 1%, by weight of the carrier.

Conveniently, pre-blended products are available containing a suitable phospholipid + solubilizing agent combination for use in compositions of the present invention. Pre-blended phospholipid + solubilizing agent products can be advantageous in improving ease of preparation of the present compositions.

An illustrative example of a pre-blended phospholipid + solubilizing agent product is Phosal 50 PG™, available from Phospholipid GmbH, Germany, which comprises, by weight, not less than 50% phosphatidylcholine, not more than 6% lysophosphatidylcholine, about 35% propylene glycol, about 3% mono- and diglycerides from sunflower oil, about 2% soy fatty acids, about 2% ethanol, and about 0.2% ascorbyl palmitate.

Another illustrative example is Phosal 53 MCT™, also available from Phospholipid GmbH, which contains, by weight, not less than 53% phosphatidylcholine, not more than 6% lysophosphatidylcholine, about 29% medium chain triglycerides, 3–6% (typically about 5%) ethanol, about 3% mono- and diglycerides from sunflower oil, about 2% oleic acid, and about 0.2% ascorbyl palmitate (reference composition). A product having the above or substantially equivalent composition, whether sold under the Phosal 53 MCT™ brand or otherwise, is generically referred to herein as “phosphatidylcholine + medium chain triglycerides 53/29”. A product having “substantially equivalent composition” in the present context means having a composition sufficiently similar to the reference composition in its ingredient list and relative amounts of ingredients to exhibit no practical difference in properties with respect to utilization of the product herein.

Yet another illustrative example is Lipoid S75™, available from Lipoid GmbH, which

contains, by weight, not less than 70% phosphatidylcholine in a solubilizing system. This can be further blended with medium-chain triglycerides, for example in a 30/70 weight/weight mixture, to provide a product ("Lipoid S75™ MCT") containing, by weight, not less than 20% phosphatidylcholine, 2–4% phosphatidylethanolamine, not more than 1.5% lysophosphatidylcholine, and 67–73% medium-chain triglycerides.

Yet another illustrative example is Phosal 50 SA+™, available from Phospholipid GmbH, which contains, by weight, not less than 50% phosphatidylcholine and not more than 6% lysophosphatidylcholine in a solubilizing system comprising safflower oil and other ingredients.

The phosphatidylcholine component of each of these pre-blended products is derived from soy lecithin. Products of substantially equivalent composition may be obtainable from other suppliers.

A pre-blended product such as Phosal 50 PG™, Phosal 53 MCT™, Lipoid S75™ MCT or Phosal 50 SA+™ can, in some embodiments, constitute substantially the entire carrier system. In other embodiments, additional ingredients are present, for example ethanol (additional to any that may be present in the pre-blended product), non-phospholipid surfactant such as polysorbate 80, polyethylene glycol and/or other ingredients. Such additional ingredients, if present, are typically included in only minor amounts. Illustratively, phosphatidylcholine + medium chain triglycerides 53/29 can be included in the carrier in an amount of about 50% to 100%, for example about 80% to 100%, by weight of the carrier.

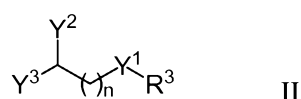
U.S. Patent Application Publication No. 2009/0149461 of Krivoshik, incorporated by reference herein without admission that it constitutes prior art to the present invention, describes a clinical trial using as study drug ABT-263 in a form of a powder for oral solution when mixed (25 mg/ml) in diluents listed as Phosal 53 MCT™ and dehydrated alcohol.

ABT-263 is susceptible to degradation in an oxidative environment; thus it will often be found desirable to include an antioxidant in the composition. Antioxidants used in pharmaceutical compositions are most typically agents that inhibit generation of oxidative species such as triplet or singlet oxygen, superoxides, peroxide and free hydroxyl radicals, or agents that scavenge such oxidative species as they are generated. Examples of commonly used antioxidants of these classes include butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), retinyl palmitate, tocopherol, propyl gallate, ascorbic acid and ascorbyl palmitate. Such antioxidants can be used; alternatively heavier-chalcogen antioxidants may be particularly useful.

A chalcogen is an element of Group 16 (formerly known as Group VIA) of the periodic

table, including oxygen, sulfur, selenium and tellurium. A “heavier-chalcogen” herein means a chalcogen having heavier atomic weight than oxygen, specifically including sulfur and selenium. A “heavier-chalcogen antioxidant” or “HCA” is a compound having antioxidant properties that contains one or more oxidizable sulfur or selenium, most particularly sulfur, atoms. HCAs are believed, without being bound by theory, to function primarily as competitive substrates, *i.e.*, as “sacrificial” antioxidants, which are preferentially attacked by oxidative species thereby protecting the drug from excessive degradation.

In some embodiments, the HCA comprises one or more antioxidant compounds of Formula II:



where

$n$  is 0, 1 or 2;

$\text{Y}^1$  is S or Se;

$\text{Y}^2$  is  $\text{NHR}^1$ , OH or H, where  $\text{R}^1$  is alkyl or alkylcarbonyl;

$\text{Y}^3$  is  $\text{COOR}^2$  or  $\text{CH}_2\text{OH}$ , where  $\text{R}^2$  is H or alkyl; and

$\text{R}^3$  is H or alkyl;

where alkyl groups are independently optionally substituted with one or more substituents independently selected from the group consisting of carboxyl, alkylcarbonyl, alkoxy carbonyl, amino and alkylcarbonylamino; a pharmaceutically acceptable salt thereof; or, where  $\text{Y}^1$  is S and  $\text{R}^3$  is H, an  $-\text{S}-\text{S}-$  dimer thereof or pharmaceutically acceptable salt of such dimer.

In other embodiments, the HCA is an antioxidant compound of Formula III:



where

Y is S, Se or  $\text{S}-\text{S}$ ; and

$\text{R}^4$  and  $\text{R}^5$  are independently selected from H, alkyl and  $(\text{CH}_2)_n\text{R}^6$  where  $n$  is 0–10 and  $\text{R}^6$  is arylcarbonyl, alkylcarbonyl, alkoxy carbonyl, carboxyl or  $\text{CHR}^7\text{R}^8$ -substituted alkyl, where  $\text{R}^7$  and  $\text{R}^8$  are independently  $\text{CO}_2\text{R}^9$ ,  $\text{CH}_2\text{OH}$ , hydrogen or  $\text{NHR}^{10}$ , where  $\text{R}^9$  is H, alkyl, substituted alkyl or arylalkyl and  $\text{R}^{10}$  is hydrogen, alkyl, alkylcarbonyl or alkoxy carbonyl.

An “alkyl” substituent or an “alkyl” or “alkoxy” group forming part of a substituent according to Formula II or Formula III is one having 1 to about 18 carbon atoms and can

consist of a straight or branched chain.

An "aryl" group forming part of a substituent according to Formula III is a phenyl group, unsubstituted or substituted with one or more hydroxy, alkoxy or alkyl groups.

In some embodiments,  $R^1$  in Formula II is  $C_{1-4}$  alkyl (*e.g.*, methyl or ethyl) or ( $C_{1-4}$  alkyl)carbonyl (*e.g.*, acetyl).

In some embodiments,  $R^2$  in Formula II is H or  $C_{1-18}$  alkyl, for example methyl, ethyl, propyl (*e.g.*, *n*-propyl or isopropyl), butyl (*e.g.*, *n*-butyl, isobutyl or *t*-butyl), octyl (*e.g.*, *n*-octyl or 2-ethylhexyl), dodecyl (*e.g.*, lauryl), tridecyl, tetradecyl, hexadecyl or octadecyl (*e.g.*, stearyl).

$R^3$  is typically H or  $C_{1-4}$  alkyl (*e.g.*, methyl or ethyl).

The HCA can be, for example, a natural or synthetic amino acid or a derivative thereof such as an alkyl ester or N-acyl derivative, or a salt of such amino acid or derivative. Where the amino acid or derivative thereof is derived from a natural source it is typically in the L-configuration; however it is understood that D-isomers and D,L-isomer mixtures can be substituted if necessary.

Non-limiting examples of HCAs useful herein include  $\beta$ -alkylmercaptoketones, cysteine, cystine, homocysteine, methionine, thiodiglycolic acid, thiodipropionic acid, thioglycerol, selenocysteine, selenomethionine and salts, esters, amides and thioethers thereof; and combinations thereof. More particularly, one or more HCAs can be selected from N-acetylcysteine, N-acetylcysteine butyl ester, N-acetylcysteine dodecyl ester, N-acetyl-cysteine ethyl ester, N-acetylcysteine methyl ester, N-acetylcysteine octyl ester, N-acetyl-cysteine propyl ester, N-acetylcysteine stearyl ester, N-acetylcysteine tetradecyl ester, N-acetylcysteine tridecyl ester, N-acetylmethionine, N-acetylmethionine butyl ester, N-acetylmethionine dodecyl ester, N-acetylmethionine ethyl ester, N-acetylmethionine methyl ester, N-acetylmethionine octyl ester, N-acetylmethionine propyl ester, N-acetylmethionine stearyl ester, N-acetylmethionine tetradecyl ester, N-acetylmethionine tridecyl ester, N-acetyl-selenocysteine, N-acetylselenocysteine butyl ester, N-acetylselenocysteine dodecyl ester, N-acetylselenocysteine ethyl ester, N-acetylselenocysteine methyl ester, N-acetylseleno-cysteine octyl ester, N-acetylselenocysteine propyl ester, N-acetylselenocysteine stearyl ester, N-acetylselenocysteine tetradecyl ester, N-acetylselenocysteine tridecyl ester, N-acetylselenomethionine, N-acetylselenomethionine butyl ester, N-acetylselenomethionine dodecyl ester, N-acetylselenomethionine ethyl ester, N-acetylselenomethionine methyl ester, N-acetylselenomethionine octyl ester, N-acetylselenomethionine propyl ester, N-acetylseleno-

methionine stearyl ester, N-acetylselenomethionine tetradecyl ester, N-acetylselenomethionine tridecyl ester, cysteine, cysteine butyl ester, cysteine dodecyl ester, cysteine ethyl ester, cysteine methyl ester, cysteine octyl ester, cysteine propyl ester, cysteine stearyl ester, cysteine tetradecyl ester, cysteine tridecyl ester, cystine, cystine dibutyl ester, cystine di(dodecyl) ester, cystine diethyl ester, cystine dimethyl ester, cystine dioctyl ester, cystine dipropyl ester, cystine distearyl ester, cystine di(tetradecyl) ester, cystine di(tridecyl) ester, N,N-diacetylcystine, N,N-diacetylcystine dibutyl ester, N,N-diacetylcystine diethyl ester, N,N-diacetylcystine di(dodecyl) ester, N,N-diacetylcystine dimethyl ester, N,N-diacetylcystine dioctyl ester, N,N-diacetylcystine dipropyl ester, N,N-diacetylcystine distearyl ester, N,N-diacetylcystine di(tetradecyl) ester, N,N-diacetylcystine di(tridecyl) ester, dibutyl thiodiglycolate, dibutyl thiodipropionate, di(dodecyl) thiodiglycolate, di(dodecyl) thiodipropionate, diethyl thiodiglycolate, diethyl thiodipropionate, dimethyl thiodiglycolate, dimethyl thiodipropionate, dioctyl thiodiglycolate, dioctyl thiodipropionate, dipropyl thiodiglycolate, dipropyl thiodipropionate, distearyl thiodiglycolate, distearyl thiodipropionate, di(tetradecyl) thiodiglycolate, di(tetradecyl) thiodipropionate, homocysteine, homocysteine butyl ester, homocysteine dodecyl ester, homocysteine ethyl ester, homocysteine methyl ester, homocysteine octyl ester, homocysteine propyl ester, homocysteine stearyl ester, homocysteine tetradecyl ester, homocysteine tridecyl ester, methionine, methionine butyl ester, methionine dodecyl ester, methionine ethyl ester, methionine methyl ester, methionine octyl ester, methionine propyl ester, methionine stearyl ester, methionine tetradecyl ester, methionine tridecyl ester, S-methylcysteine, S-methylcysteine butyl ester, S-methylcysteine dodecyl ester, S-methylcysteine ethyl ester, S-methylcysteine methyl ester, S-methylcysteine octyl ester, S-methylcysteine propyl ester, S-methylcysteine stearyl ester, S-methylcysteine tetradecyl ester, S-methylcysteine tridecyl ester, selenocysteine, selenocysteine butyl ester, selenocysteine dodecyl ester, selenocysteine ethyl ester, selenocysteine methyl ester, selenocysteine octyl ester, selenocysteine propyl ester, selenocysteine stearyl ester, selenocysteine tetradecyl ester, selenocysteine tridecyl ester, selenomethionine, selenomethionine butyl ester, selenomethionine dodecyl ester, selenomethionine ethyl ester, selenomethionine methyl ester, selenomethionine octyl ester, selenomethionine propyl ester, selenomethionine stearyl ester, selenomethionine tetradecyl ester, selenomethionine tridecyl ester, thiodiglycolic acid, thiodipropionic acid, thioglycerol, isomers and mixtures of isomers thereof, and salts thereof.

Salts of HCA compounds can be acid addition salts such as the acetate, adipate, alginate, bicarbonate, citrate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate,

butyrate, camphorate, camphorsulfonate, digluconate, formate, fumarate, glycerophosphate, glutamate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, lactobionate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, phosphate, picrate, propionate, succinate, tartrate, thiocyanate, trichloroacetate, trifluoroacetate, para-toluenesulfonate and undecanoate salts. In a particular embodiment, the hydrochloride salt of one of the compounds individually mentioned above is present in the composition in an antioxidant effective amount.

Without being bound by theory, it is generally believed that heavier-chalcogen antioxidants such as those exemplified above protect ABT-263 by being themselves more readily oxidizable and, therefore, being oxidized preferentially over the ABT-263. In general, for this mode of operation to provide an acceptable degree of protection for ABT-263, an antioxidant of Formula II or Formula III must be present in a substantial amount, for example in a molar ratio to ABT-263 of at least about 1:10. In some embodiments, the molar ratio of antioxidant to ABT-263 is about 1:10 to about 2:1, for example about 1:5 to about 1.5:1. Best results will sometimes be obtained when the molar ratio is approximately 1:1, *i.e.*, about 8:10 to about 10:8.

Notwithstanding the antioxidant efficacy of sulfur-containing antioxidants of Formula II or Formula III, it has been found that, at molar ratios of approximately 1:1, such antioxidants have a tendency to result in solutions that become cloudy upon storage, when ABT-263 is used in the form of its free base.

However, ABT-263 free base has been found to be less susceptible to sulfoxide formation than ABT-263 in salt form, for example ABT-263 *bis*-HCl, when formulated in lipid solution (but in the absence of antioxidant). To take advantage of this finding, a different class of sulfur-containing antioxidants can be used with ABT-263 free base, namely inorganic antioxidants of the sulfite, bisulfite, metabisulfite and thiosulfate classes. To complicate matters, these antioxidants are poorly lipid-soluble and, where a liquid formulation is desired, must be introduced to the carrier or drug-carrier system in aqueous solution. Presence of water promotes sulfoxide formation in ABT-263 solutions, the very effect that is sought to be minimized. To restrict the amount of added water, poorly lipid-soluble antioxidants are, in one embodiment of the present invention, added at much lower concentrations than those providing molar equivalence to the concentration of ABT-263.

Where a poorly lipid-soluble antioxidant such as a sulfite, bisulfite, metabisulfite or thiosulfate antioxidant is used, it is accompanied in the drug-carrier system by water in an



amount not exceeding about 1% by weight, for example about 0.2% to about 0.8% by weight. The amount of such antioxidant that can be introduced in such a small amount of water typically does not exceed about 0.2% by weight, and is for example an amount of about 0.02% to about 0.2%, or about 0.05% to about 0.15%, by weight, of the drug-carrier system.

To minimize the amount of water added to the formulation, it is desirable to provide the antioxidant in the form of a relatively concentrated aqueous stock solution, for example having at least about 10% by weight antioxidant. However, it has been found that where an excessively concentrated stock solution (*e.g.*, about 20% or higher) is used, this can result in undesirable precipitation of solids in the formulation. Suitable concentrations of antioxidant in the stock solution are typically about 10% to about 18%, illustratively about 15%, by weight.

Sodium and potassium salts of sulfites, bisulfites, metabisulfites and thiosulfates are useful antioxidants according to the present embodiment; more particularly sodium and potassium metabisulfites.

To further minimize sulfoxide formation, a chelating agent such as EDTA or a salt thereof (*e.g.*, disodium EDTA or calcium disodium EDTA) is optionally added, for example in an amount of about 0.002% to about 0.02% by weight of the drug-carrier system. EDTA can be added as an aqueous stock solution in the same manner as the antioxidant. The antioxidant and EDTA can, if desired, be added as components of the same stock solution. Chelating agents sequester metal ions that can promote oxidative degradation.

Even at the very low antioxidant concentrations contemplated herein (typically the molar ratio of poorly lipid-soluble antioxidant to ABT-263 according to the present embodiment is no greater than about 1:20), sulfoxide formation has been found to remain within acceptable limits.

Sulfoxide formation can be further minimized by selecting formulation ingredients having low peroxide value. Peroxide value is a well established property of pharmaceutical excipients and is generally expressed (as herein) in units corresponding to milliequivalents of peroxides per kilogram of excipient (meq/kg). Some excipients inherently have low peroxide value, but others, for example those having unsaturated fatty acid such as oleyl moieties and/or polyoxyethylene chains, can be sources of peroxides. In the case of polysorbate 80, for example, it is preferable to select a source of polysorbate 80 having a peroxide value not greater than about 5, for example not greater than about 2. Suitable sources include Crillet 4HPT<sup>TM</sup> and Super-Refined Tween 80<sup>TM</sup>, both available from Croda.

Without being bound by theory, it is believed that the therapeutic efficacy of ABT-263

is due at least in part to its ability to bind to a Bcl-2 family protein such as Bcl-2, Bcl-X<sub>L</sub> or Bcl-w in a way that inhibits the anti-apoptotic action of the protein, for example by occupying the BH3 binding groove of the protein.

In still further embodiments of the invention, there is provided a method for treating a disease characterized by apoptotic dysfunction and/or overexpression of an anti-apoptotic Bcl-2 family protein, comprising administering to a subject having the disease a therapeutically effective amount of crystalline ABT-263 free base or a pharmaceutical composition comprising crystalline ABT-263 free base and one or more pharmaceutically acceptable excipients. In one embodiment, the method comprises administering to the subject crystalline Form I ABT-263 free base or a pharmaceutical composition comprising crystalline Form I ABT-263 free base and one or more pharmaceutically acceptable excipients. In another embodiment, the method comprises administering to the subject crystalline Form II ABT-263 free base or a pharmaceutical composition comprising crystalline Form II ABT-263 free base and one or more pharmaceutically acceptable excipients.

In still further embodiments of the invention, there is provided a method for treating a disease characterized by apoptotic dysfunction and/or overexpression of an anti-apoptotic Bcl-2 family protein, comprising (a) dissolving crystalline ABT-263 free base in a pharmaceutically acceptable solvent or mixture of solvents (for example selected from such solvents mentioned as excipients hereinabove), and (b) administering the resulting solution in a therapeutically effective amount to a subject having the disease. In one embodiment, the crystalline ABT-263 free base is crystalline Form I ABT-263 free base. In another embodiment, the crystalline ABT-263 free base is crystalline Form II ABT-263 free base.

The subject can be human or non-human (*e.g.*, a farm, zoo, work or companion animal, or a laboratory animal used as a model) but in an important embodiment the subject is a human patient in need of the drug, for example to treat a disease characterized by apoptotic dysfunction and/or overexpression of an anti-apoptotic Bcl-2 family protein. A human subject can be male or female and of any age. The patient is typically an adult, but a method of the invention can be useful to treat a childhood cancer such as leukemia, for example acute lymphocytic leukemia, in a pediatric patient.

The composition is normally administered in an amount providing a therapeutically effective daily dose of the drug. The term "daily dose" herein means the amount of drug administered per day, regardless of the frequency of administration. For example, if the subject receives a unit dose of 150 mg twice daily, the daily dose is 300 mg. Use of the term

“daily dose” will be understood not to imply that the specified dosage amount is necessarily administered once daily. However, in a particular embodiment the dosing frequency is once daily (q.d.), and the daily dose and unit dose are in this embodiment the same thing.

What constitutes a therapeutically effective dose depends on the bioavailability of the particular formulation, the subject (including species and body weight of the subject), the disease (*e.g.*, the particular type of cancer) to be treated, the stage and/or severity of the disease, the individual subject’s tolerance of the compound, whether the compound is administered in monotherapy or in combination with one or more other drugs, *e.g.*, other chemotherapeutics for treatment of cancer, and other factors. Thus the daily dose can vary within wide margins, for example from about 10 to about 1,000 mg. Greater or lesser daily doses can be appropriate in specific situations. It will be understood that recitation herein of a “therapeutically effective” dose herein does not necessarily require that the drug be therapeutically effective if only a single such dose is administered; typically therapeutic efficacy depends on the composition being administered repeatedly according to a regimen involving appropriate frequency and duration of administration. It is strongly preferred that, while the daily dose selected is sufficient to provide benefit in terms of treating the cancer, it should not be sufficient to provoke an adverse side-effect to an unacceptable or intolerable degree. A suitable therapeutically effective dose can be selected by the physician of ordinary skill without undue experimentation based on the disclosure herein and on art cited herein, taking into account factors such as those mentioned above. The physician may, for example, start a cancer patient on a course of therapy with a relatively low daily dose and titrate the dose upwards over a period of days or weeks, to reduce risk of adverse side-effects.

Illustratively, suitable doses of ABT-263 are generally about 25 to about 1000 mg/day or about 50 to about 1000 mg/day, more typically about 50 to about 500 mg/day or about 200 to about 400 mg/day, for example about 50, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450, about 500, about 750 or about 1000 mg/day, administered at an average dosage interval of about 3 hours to about 7 days, for example about 8 hours to about 3 days, or about 12 hours to about 2 days. In most cases a once-daily (q.d.) administration regimen is suitable.

An “average dosage interval” herein is defined as a span of time, for example one day or one week, divided by the number of unit doses administered over that span of time. For example, where a drug is administered three times a day, around 8 am, around noon and around 6 pm, the average dosage interval is 8 hours (a 24-hour time span divided by 3). If the drug is formulated as a discrete dosage form such as a tablet or capsule, a plurality (*e.g.*, 2

to about 10) of dosage forms administered at one time is considered a unit dose for the purpose of defining the average dosage interval.

A daily dosage amount and dosage interval can, in some embodiments, be selected to maintain a plasma concentration of ABT-263 in a range of about 0.5 to about 10 µg/ml. Thus, during a course of ABT-263 therapy according to such embodiments, the steady-state peak plasma concentration ( $C_{\max}$ ) should in general not exceed about 10 µg/ml, and the steady-state trough plasma concentration ( $C_{\min}$ ) should in general not fall below about 0.5 µg/ml. It will further be found desirable to select, within the ranges provided above, a daily dosage amount and average dosage interval effective to provide a  $C_{\max}/C_{\min}$  ratio not greater than about 5, for example not greater than about 3, at steady-state. It will be understood that longer dosage intervals will tend to result in greater  $C_{\max}/C_{\min}$  ratios. Illustratively, at steady-state, an ABT-263  $C_{\max}$  of about 3 to about 8 µg/ml and  $C_{\min}$  of about 1 to about 5 µg/ml can be targeted by the present method. Steady-state values of  $C_{\max}$  and  $C_{\min}$  can be established in a human PK study, for example conducted according to standard protocols including but not limited to those acceptable to a regulatory agency such as the U.S. Food and Drug Administration (FDA).

As compositions useful herein are believed to exhibit only a minor food effect, administration according to the present embodiment can be with or without food, *i.e.*, in a non-fasting or fasting condition. It is generally preferred to administer the present compositions to a non-fasting patient.

Formulations of the present invention are suitable for use in monotherapy or in combination therapy, for example with other chemotherapeutics or with ionizing radiation. A particular advantage of the present invention is that it permits once-daily oral administration, a regimen which is convenient for the patient who is undergoing treatment with other orally administered drugs on a once-daily regimen. Oral administration is easily accomplished by the patient him/herself or by a caregiver in the patient's home; it is also a convenient route of administration for patients in a hospital or residential care setting.

Combination therapies illustratively include administration of a composition comprising (or prepared using as API) crystalline ABT-263 free base concomitantly with one or more of bortezomid, carboplatin, cisplatin, cyclophosphamide, dacarbazine, dexamethasone, docetaxel, doxorubicin, etoposide, fludarabine, hydroxydoxorubicin, irinotecan, paclitaxel, rapamycin, rituximab, vincristine and the like, for example with a polytherapy such as CHOP (cyclophosphamide + hydroxydoxorubicin + vincristine + prednisone), RCVP (rituximab + cyclophosphamide + vincristine + prednisone), R-CHOP (rituximab + CHOP) or DA-

EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab).

An ABT-263 composition can be administered in combination therapy with one or more therapeutic agents that include, but are not limited to, angiogenesis inhibitors, antiproliferative agents, other apoptosis promoters (for example, Bcl-xL, Bcl-w and Bfl-1 inhibitors), activators of a death receptor pathway, BiTE (bi-specific T-cell engager) antibodies, dual variable domain binding proteins (DVDs), inhibitors of apoptosis proteins (IAPs), microRNAs, mitogen-activated extracellular signal-regulated kinase inhibitors, multivalent binding proteins, poly-ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, small inhibitory ribonucleic acids (siRNAs), kinase inhibitors, receptor tyrosine kinase inhibitors, aurora kinase inhibitors, polo-like kinase inhibitors, bcr-abl kinase inhibitors, growth factor inhibitors, COX-2 inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), antimetabolic agents, alkylating agents, antimetabolites, intercalating antibiotics, platinum-containing chemotherapeutic agents, growth factor inhibitors, ionizing radiation, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biologic response modifiers, immunologicals, antibodies, hormonal therapies, retinoids, deltidoids, plant alkaloids, proteasome inhibitors, HSP-90 inhibitors, histone deacetylase (HDAC) inhibitors, purine analogs, pyrimidine analogs, MEK inhibitors, CDK inhibitors, ErbB2 receptor inhibitors, mTOR inhibitors as well as other antitumor agents.

Angiogenesis inhibitors include, but are not limited to, EGFR inhibitors, PDGFR inhibitors, VEGFR inhibitors, TIE2 inhibitors, IGF1R inhibitors, matrix metalloproteinase 2 (MMP-2) inhibitors, matrix metalloproteinase 9 (MMP-9) inhibitors and thrombospondin analogs.

Examples of EGFR inhibitors include, but are not limited to, gefitinib, erlotinib, cetuximab, EMD-7200, ABX-EGF, HR3, IgA antibodies, TP-38 (IVAX), EGFR fusion protein, EGF-vaccine, anti-EGFR immunoliposomes and lapatinib.

Examples of PDGFR inhibitors include, but are not limited to, CP-673451 and CP-868596.

Examples of VEGFR inhibitors include, but are not limited to, bevacizumab, sunitinib, sorafenib, CP-547632, axitinib, vandetanib, AEE788, AZD-2171, VEGF trap, vatalanib, pegaptanib, IM862, pazopanib, ABT-869 and angiozyme.

Bcl-2 family protein inhibitors other than ABT-263 or compounds of Formula I herein include, but are not limited to, AT-101 ((-)-gossypol), Genasense™ Bcl-2-targeting antisense oligonucleotide (G3139 or oblimersen), IPI-194, IPI-565, ABT-737, GX-070 (obatoclax) and

the like.

Activators of a death receptor pathway include, but are not limited to, TRAIL, antibodies or other agents that target death receptors (*e.g.*, DR4 and DR5) such as apomab, conatumumab, ETR2-ST01, GDC0145 (lexatumumab), HGS-1029, LBY-135, PRO-1762 and trastuzumab.

Examples of thrombospondin analogs include, but are not limited to, TSP-1, ABT-510, ABT-567 and ABT-898.

Examples of aurora kinase inhibitors include, but are not limited to, VX-680, AZD-1152 and MLN-8054.

An example of a polo-like kinase inhibitor includes, but is not limited to, BI-2536.

Examples of bcr-abl kinase inhibitors include, but are not limited to, imatinib and dasatinib.

Examples of platinum-containing agents include, but are not limited to, cisplatin, carboplatin, eptaplatin, lobaplatin, nedaplatin, oxaliplatin and satraplatin.

Examples of mTOR inhibitors include, but are not limited to, CCI-779, rapamycin, temsirolimus, everolimus, RAD001 and AP-23573.

Examples of HSP-90 inhibitors include, but are not limited to, geldanamycin, radicicol, 17-AAG, KOS-953, 17-DMAG, CNF-101, CNF-1010, 17-AAG-nab, NCS-683664, efungumab, CNF-2024, PU3, PU24FCI, VER-49009, IPI-504, SNX-2112 and STA-9090.

Examples of HDAC inhibitors include, but are not limited to, suberoylanilide hydroxamic acid (SAHA), MS-275, valproic acid, TSA, LAQ-824, trapoxin and depsipeptide.

Examples of MEK inhibitors include, but are not limited to, PD-325901, ARRY-142886, ARRY-438162 and PD-98059.

Examples of CDK inhibitors include, but are not limited to, flavopyridol, MCS-5A, CVT-2584, seliciclib ZK-304709, PHA-690509, BMI-1040, GPC-286199, BMS-387032, PD-332991 and AZD-5438.

Examples of COX-2 inhibitors include, but are not limited to, celecoxib, parecoxib, deracoxib, ABT-963, etoricoxib, lumiracoxib, BMS-347070, RS 57067, NS-398, valdecoxib, rofecoxib, SD-8381, 4-methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoylphenyl)-1H-pyrrole, T-614, JTE-522, S-2474, SVT-2016, CT-3 and SC-58125.

Examples of NSAIDs include, but are not limited to, salsalate, diflunisal, ibuprofen, ketoprofen, nabumetone, piroxicam, naproxen, diclofenac, indomethacin, sulindac, tolmetin, etodolac, ketorolac and oxaprozin.

Examples of ErbB2 receptor inhibitors include, but are not limited to, CP-724714, canertinib, trastuzumab, petuzumab, TAK-165, ionafamib, GW-282974, EKB-569, PI-166, dHER2, APC-8024, anti-HER/2neu bispecific antibody B7.her2IgG3 and HER2 trifunctional bispecific antibodies mAB AR-209 and mAB 2B-1.

Examples of alkylating agents include, but are not limited to, nitrogen mustard N-oxide, cyclophosphamide, ifosfamide, trofosfamide, chlorambucil, melphalan, busulfan, mitobronitol, carboquone, thiotepa, ranimustine, nimustine, Cloretazine™ (laromustine), AMD-473, altretamine, AP-5280, apaziquone, brostallicin, bendamustine, carmustine, estramustine, fotemustine, glufosfamide, KW-2170, mafosfamide, mitolactol, lomustine, treosulfan, dacarbazine and temozolomide.

Examples of antimetabolites include, but are not limited to, methotrexate, 6-mercaptopurine riboside, mercaptopurine, 5-fluorouracil (5-FU) alone or in combination with leucovorin, tegafur, UFT, doxifluridine, carmofur, cytarabine, cytarabine ocfosfate, enocitabine, S-1, pemetrexed, gemcitabine, fludarabine, 5-azacitidine, capecitabine, cladribine, clofarabine, decitabine, eflornithine, ethenylcytidine, cytosine arabinoside, hydroxyurea, TS-1, melphalan, nelarabine, nolatrexed, disodium pemetrexed, pentostatin, pelitrexol, raltitrexed, triapine, trimetrexate, vidarabine, mycophenolic acid, ocfosfate, pentostatin, tiazofurin, ribavirin, EICAR, hydroxyurea and deferoxamine.

Examples of antibiotics include, but are not limited to, intercalating antibiotics, aclarubicin, actinomycin D, amrubicin, annamycin, adriamycin, bleomycin, daunorubicin, doxorubicin (including liposomal doxorubicin), elsamitrucin, epirubicin, glarubicin, idarubicin, mitomycin C, nemorubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, valrubicin, zinostatin and combinations thereof.

Examples of topoisomerase inhibiting agents include, but are not limited to, aclarubicin, amonafide, belotecan, camptothecin, 10-hydroxycamptothecin, 9-amino-camptothecin, amsacrine, dexrazoxane, diflomotecan, irinotecan HCl, edotecarin, epirubicin, etoposide, exatecan, becatecarin, gimatecan, lurtotecan, orathecin, BN-80915, mitoxantrone, pirarubicin, pixantrone, rubitecan, sobuzoxane, SN-38, tafluposide and topotecan.

Examples of antibodies include, but are not limited to, rituximab, cetuximab, bevacizumab, trastuzumab, CD40-specific antibodies and IGF1R-specific antibodies, chTNT-1/B, denosumab, edrecolomab, WX G250, zanolimumab, lintuzumab and ticilimumab.

Examples of hormonal therapies include, but are not limited to, sevelamer carbonate, rilostane, luteinizing hormone releasing hormone, modrastane, exemestane, leuprolide acetate, buserelin, cetrorelix, deslorelin, histrelin, anastrozole, fosreltin, goserelin, degarelix,

doxercalciferol, fadrozole, formestane, tamoxifen, arzoxifene, bicalutamide, abarelix, triptorelin, finasteride, fulvestrant, toremifene, raloxifene, trilostane, lasofoxifene, letrozole, flutamide, megestrol, mifepristone, nilutamide, dexamethasone, prednisone and other glucocorticoids.

Examples of retinoids or deltoids include, but are not limited to, seocalcitol, lexacalcitol, fenretinide, aliretinoin, tretinoin, bexarotene and LGD-1550.

Examples of plant alkaloids include, but are not limited to, vincristine, vinblastine, vindesine and vinorelbine.

Examples of proteasome inhibitors include, but are not limited to, bortezomib, MG-132, NPI-0052 and PR-171.

Examples of immunologicals include, but are not limited to, interferons and numerous other immune-enhancing agents. Interferons include interferon alpha, interferon alpha-2a, interferon alpha-2b, interferon beta, interferon gamma-1a, interferon gamma-1b, interferon gamma-n1 and combinations thereof. Other agents include filgrastim, lentinan, sizofilan, BCG live, ubenimex, WF-10 (tetrachlorodecaoxide or TCDO), aldesleukin, alemtuzumab, BAM-002, dacarbazine, daclizumab, denileukin, gemtuzumab, ozogamicin, ibritumomab, imiquimod, lenograstim, melanoma vaccine, molgramostim, sargaramostim, tasonermin, teceleukin, thymalasin, tositumomab, Virulizin™ immunotherapeutic of Lorus Pharmaceuticals, Z-100 (specific substance of Maruyama or SSM), Zevalin™ (90Y-ibritumomab tiuxetan), epratuzumab, mitumomab, oregovomab, pemtumomab, Provenge™ (sipuleucel-T), teceleukin, Therocys™ (Bacillus Calmette-Guerin), cytotoxic lymphocyte antigen 4 (CTLA4) antibodies and agents capable of blocking CTLA4 such as MDX-010.

Examples of biological response modifiers are agents that modify defense mechanisms of living organisms or biological responses, such as survival, growth, or differentiation of tissue cells to direct them to have anti-tumor activity. Such agents include, but are not limited to, krestin, lentinan, sizofuran, picibanil, PF-3512676 and ubenimex.

Examples of pyrimidine analogs include, but are not limited to, 5-fluorouracil, floxuridine, doxifluridine, raltitrexed, cytarabine, cytosine arabinoside, fludarabine, triacetylrudine, troxacitabine and gemcitabine.

Examples of purine analogs include, but are not limited to, mercaptopurine and thioguanine.

Examples of antimitotic agents include, but are not limited to, N-(2-((4-hydroxyphenyl)amino)pyridin-3-yl)-4-methoxybenzenesulfonamide, paclitaxel, docetaxel, larotaxel, epothilone D, PNU-100940, batabulin, ixabepilone, patupilone, XRP-9881,



vinflunine and ZK-EPO (synthetic epoethilone).

Examples of radiotherapy include, but are not limited to, external beam radiotherapy (XBRT), teletherapy, brachytherapy, sealed-source radiotherapy and unsealed-source radiotherapy.

BiTE antibodies are bi-specific antibodies that direct T-cells to attack cancer cells by simultaneously binding the two cells. The T-cell then attacks the target cancer cell. Examples of BiTE antibodies include, but are not limited to, adecatumumab (Micromet MT201), blinatumomab (Micromet MT103) and the like. Without being limited by theory, one of the mechanisms by which T-cells elicit apoptosis of the target cancer cell is by exocytosis of cytolytic granule components, which include perforin and granzyme B. In this regard, Bcl-2 has been shown to attenuate the induction of apoptosis by both perforin and granzyme B. These data suggest that inhibition of Bcl-2 could enhance the cytotoxic effects elicited by T-cells when targeted to cancer cells (Sutton *et al.* (1997) J. Immunol. 158:5783–5790).

SiRNAs are molecules having endogenous RNA bases or chemically modified nucleotides. The modifications do not abolish cellular activity, but rather impart increased stability and/or increased cellular potency. Examples of chemical modifications include phosphorothioate groups, 2'-deoxynucleotide, 2'-OCH<sub>3</sub>-containing ribonucleotides, 2'-F-ribonucleotides, 2'-methoxyethyl ribonucleotides, combinations thereof and the like. The siRNA can have varying lengths (*e.g.*, 10–200 bps) and structures (*e.g.*, hairpins, single/double strands, bulges, nicks/gaps, mismatches) and are processed in cells to provide active gene silencing. A double-stranded siRNA (dsRNA) can have the same number of nucleotides on each strand (blunt ends) or asymmetric ends (overhangs). The overhang of 1–2 nucleotides can be present on the sense and/or the antisense strand, as well as present on the 5'- and/ or the 3'-ends of a given strand. For example, siRNAs targeting Mcl-1 have been shown to enhance the activity of ABT-263 (Tse *et al.* (2008), *supra*, and references therein).

Multivalent binding proteins are binding proteins comprising two or more antigen binding sites. Multivalent binding proteins are engineered to have the three or more antigen binding sites and are generally not naturally occurring antibodies. The term “multispecific binding protein” means a binding protein capable of binding two or more related or unrelated targets. Dual variable domain (DVD) binding proteins are tetravalent or multivalent binding proteins comprising two or more antigen binding sites. Such DVDs may be monospecific (*i.e.*, capable of binding one antigen) or multispecific (*i.e.*, capable of binding

two or more antigens). DVD binding proteins comprising two heavy-chain DVD polypeptides and two light-chain DVD polypeptides are referred to as DVD Ig's. Each half of a DVD Ig comprises a heavy-chain DVD polypeptide, a light-chain DVD polypeptide, and two antigen binding sites. Each binding site comprises a heavy-chain variable domain and a light-chain variable domain with a total of 6 CDRs involved in antigen binding per antigen binding site.

PARP inhibitors include, but are not limited to, ABT-888, olaparib, KU-59436, AZD-2281, AG-014699, BSI-201, BGP-15, INO-1001, ONO-2231 and the like.

Additionally or alternatively, a composition comprising (or prepared using as API) crystalline ABT-263 free base can be administered in combination therapy with one or more antitumor agents selected from ABT-100, N-cetylcolchicol-O-phosphate, acitretin, AE-941, aglycon protopanaxadiol, arglabin, arsenic trioxide, AS04 adjuvant-adsorbed HPV vaccine, L-asparaginase, atamestane, atrasentan, AVE-8062, bosentan, canfosfamide, Canvaxin™, catumaxomab, CeaVac™, celmoleukin, combrestatin A4P, contusugene ladenovec, Cotara™, cyproterone, deoxycoformycin, dexrazoxane, N,N-diethyl-2-(4-(phenylmethyl)phenoxy) ethanamine, 5,6-dimethylxanthenone-4-acetic acid, docosahexaenoic acid/paclitaxel, discodermolide, efaproxiral, enzastaurin, epothilone B, ethynyluracil, exisulind, falimarev, Gastrimmune™, GMK vaccine, GVAX™, halofuginone, histamine, hydroxycarbamide, ibandronic acid, ibritumomab tiuxetan, IL-13-PE38, inalimarev, interleukin 4, KSB-311, lanreotide, lenalidomide, lonafarnib, lovastatin, 5,10-methylenetetrahydrofolate, mifamurtide, miltefosine, motexafin, oblimersen, OncoVAX™, Osidem™, paclitaxel albumin-stabilized nanoparticle, paclitaxel poliglumex, pamidronate, panitumumab, peginterferon alfa, pegaspargase, phenoxodiol, poly(I)-poly(C12U), procarbazine, ranpirnase, rebimastat, recombinant quadrivalent HPV vaccine, squalamine, staurosporine, STn-KLH vaccine, T4 endonuclease V, tazarotene, 6,6',7,12-tetramethoxy-2,2'-dimethyl-1 $\beta$ -berbaman, thalidomide, TNFerade™, <sup>131</sup>I-tositumomab, trabectedin, triazone, tumor necrosis factor, Ukrain™, vaccinia-MUC-1 vaccine, L-valine-L-boroproline, Vitaxin™, vitespen, zoledronic acid and zorubicin.

In one embodiment, a composition comprising (or prepared using as API) crystalline ABT-263 free base is administered in a therapeutically effective amount to a subject in need thereof to treat a disease during which is overexpressed one or more of antiapoptotic Bcl-2 protein, antiapoptotic Bcl-X<sub>L</sub> protein and antiapoptotic Bcl-w protein.

In another embodiment, a composition comprising (or prepared using as API) crystalline ABT-263 free base is administered in a therapeutically effective amount to a

subject in need thereof to treat a disease of abnormal cell growth and/or dysregulated apoptosis.

Examples of such diseases include, but are not limited to, cancer, mesothelioma, bladder cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, bone cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal and/or duodenal) cancer, chronic lymphocytic leukemia, acute lymphocytic leukemia, esophageal cancer, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, hepatocellular (hepatic and/or biliary duct) cancer, primary or secondary central nervous system tumor, primary or secondary brain tumor, Hodgkin's disease, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphoma, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, multiple myeloma, oral cancer, non-small-cell lung cancer, prostate cancer, small-cell lung cancer, cancer of the kidney and/or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system, primary central nervous system lymphoma, non Hodgkin's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, cancer of the spleen, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma or a combination thereof.

In a more particular embodiment, a composition comprising (or prepared using as API) crystalline ABT-263 free base is administered in a therapeutically effective amount to a subject in need thereof to treat bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, acute lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small-cell lung cancer, prostate cancer, small-cell lung cancer or spleen cancer.

According to any of these embodiments, the composition can be administered in monotherapy or in combination therapy with one or more additional therapeutic agents.

For example, a method for treating mesothelioma, bladder cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the

endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, bone cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal and/or duodenal) cancer, chronic lymphocytic leukemia, acute lymphocytic leukemia, esophageal cancer, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, hepatocellular (hepatic and/or biliary duct) cancer, primary or secondary central nervous system tumor, primary or secondary brain tumor, Hodgkin's disease, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphoma, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, multiple myeloma, oral cancer, non-small-cell lung cancer, prostate cancer, small-cell lung cancer, cancer of the kidney and/or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system, primary central nervous system lymphoma, non Hodgkin's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, cancer of the spleen, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma or a combination thereof in a subject comprises administering to the subject therapeutically effective amounts of (a) a composition comprising (or prepared using as API) crystalline ABT-263 free base and (b) one or more of etoposide, vincristine, CHOP, rituximab, rapamycin, R-CHOP, RCVP, DA-EPOCH-R or bortezomib.

In particular embodiments, a composition comprising (or prepared using as API) crystalline ABT-263 free base is administered in a therapeutically effective amount to a subject in need thereof in combination therapy with etoposide, vincristine, CHOP, rituximab, rapamycin, R-CHOP, RCVP, DA-EPOCH-R or bortezomib in a therapeutically effective amount, for treatment of a lymphoid malignancy such as B-cell lymphoma or non-Hodgkin's lymphoma.

In other particular embodiments, a composition comprising (or prepared using as API) crystalline ABT-263 free base is administered in a therapeutically effective amount to a subject in need thereof in monotherapy or in combination therapy with etoposide, vincristine, CHOP, rituximab, rapamycin, R-CHOP, RCVP, DA-EPOCH-R or bortezomib in a therapeutically effective amount, for treatment of chronic lymphocytic leukemia or acute lymphocytic leukemia.

Further information of relevance to the present invention is available in a recently published article by Tse *et al.* (2008) Cancer Res. 68:3421–3428 and supplementary data

thereto available at Cancer Research Online ([cancerres.aacrjournals.org/](http://cancerres.aacrjournals.org/)). This article and its supplementary data are incorporated in their entirety herein by reference.

**CLAIMS**

1. The compound N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)-benzenesulfonamide free base in a solid crystalline Form I, characterized at least by a powder X-ray diffraction peak at any one or more of the following positions: 6.21, 6.72, 12.17, 18.03 and 20.10° 2 $\theta$ ,  $\pm$  0.2° 2 $\theta$ .
2. The compound of Claim 1, wherein the crystalline Form I is characterized at least by a powder X-ray diffraction peak at each of said positions.
3. The compound of Claim 1, wherein the crystalline Form I is characterized at least by a powder X-ray diffraction peak at each of the following positions: 6.21, 6.72, 9.66, 10.92, 11.34, 12.17, 14.28, 16.40, 16.95, 17.81, 18.03, 18.47, 19.32, 20.10 and 21.87° 2 $\theta$ ,  $\pm$  0.2° 2 $\theta$ .
4. The compound N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)-benzenesulfonamide free base in a solid crystalline Form II, characterized at least by a powder X-ray diffraction peak at any one or more of the following positions: 5.79, 8.60, 12.76, 15.00 and 20.56° 2 $\theta$ ,  $\pm$  0.2° 2 $\theta$ .
5. The compound of Claim 4, wherein the crystalline Form II is characterized at least by a powder X-ray diffraction peak at each of said positions.
6. The compound of Claim 4, wherein the crystalline Form II is characterized at least by a powder X-ray diffraction peak at each of the following positions: 5.79, 8.60, 9.34, 10.79, 11.36, 11.59, 12.76, 13.23, 13.73, 14.01, 14.72, 15.00, 16.28, 17.07,

17.48, 18.75, 19.34, 19.71, 20.56 and 21.35° 2 $\theta$ ,  $\pm$  0.2° 2 $\theta$ .

7. The compound N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)-benzenesulfonamide free base in a solid crystalline form, wherein the crystalline form is a solvate comprising the compound solvated with an organic solvent.
8. The compound of Claim 7, wherein the solvate is selected from the group consisting of ethanol/ethyl acetate mixture, 1-propanol, 2-propanol, methanol, benzene, toluene, dioxane/hexanes mixture, methyl acetate/hexanes mixture, chloroform, ethyl acetate, isopropyl acetate, methyl acetate, pyridine, anisole and trifluorotoluene solvates.
9. A pharmaceutical composition comprising the compound of any one of claims 1, 4 and 7 in a solid crystalline form and one or more pharmaceutically acceptable excipients.
10. A process for preparing a pharmaceutical solution composition of ABT-263, comprising dissolving the compound of any one of claims 1, 4 and 7 in a pharmaceutically acceptable solvent or mixture of solvents.
11. Use of the compound of any one of claims 1, 4 and 7 and one or more pharmaceutically acceptable excipients in the manufacture of a medicament comprising a therapeutically effective amount of the compound of any one of claims 1, 4 and 7 for the treatment of a neoplastic disease selected from the group consisting of cancer, mesothelioma, bladder cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma

of the vulva, bone cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal and/or duodenal) cancer, chronic lymphocytic leukemia, acute lymphocytic leukemia, esophageal cancer, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, hepatocellular (hepatic and/or biliary duct cancer, primary or secondary central nervous system tumor, primary or secondary brain tumor, Hodgkin's disease, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphoma, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, multiple myeloma, oral cancer, non-small-cell lung cancer, prostate cancer, small-cell lung cancer, cancer of the kidney and/or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system, primary central nervous system lymphoma, non-Hodgkin's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, cancer of the spleen, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma and combinations thereof.

12. The use of Claim 11, wherein the medicament comprises the compound of claim 1.
13. The use of Claim 11, wherein the medicament comprises the compound of claim 4.
14. The use of Claim 11, wherein the medicament comprises the compound of claim 7.
15. The use of Claim 14, wherein the solvate is selected from the group consisting of ethanol/ethyl acetate mixture, 1-propanol, 2-propanol, methanol, benzene, toluene, dioxane/hexanes mixture, methyl acetate/hexanes mixture, chloroform, ethyl acetate, isopropyl acetate, methyl acetate, pyridine, anisole and trifluorotoluene solvates.



16. The use of Claim 11, wherein the crystalline ABT-263 free base or pharmaceutical composition is administered by an oral, parenteral, sublingual, buccal, intranasal, pulmonary, topical, transdermal, intradermal, ocular, otic, rectal, vaginal, intragastric, intracranial, intrasynovial or intra-articular route.
17. The use of Claim 11, wherein the neoplastic disease is a lymphoid malignancy.
18. The use of Claim 17, wherein the lymphoid malignancy is non-Hodgkin's lymphoma.
19. The use of Claim 11, wherein the medicament is suitable for oral administration in a dose of about 50 to about 1000 mg ABT-263 per day at an average treatment interval of about 3 hours to about 7 days.
20. The use of Claim 11, wherein the medicament is suitable for oral administration once daily in a dose of about 200 to about 400 mg ABT-263 free base equivalent per day.
21. Use of the compound of any one of claims 1, 4 and 7 in the manufacture of a medicament for the treatment of a neoplastic disease, wherein said manufacture comprises dissolving the compound of any one of claims 1, 4 and 7 in a pharmaceutically acceptable solvent or mixture of solvents, and wherein said neoplastic disease selected from the group consisting of cancer, mesothelioma, bladder cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, breast cancer, uterine rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal and/or duodenal) cancer, chronic lymphocytic leukemia, acute lymphocytic leukemia, esophageal cancer, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the

adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, hepatocellular (hepatic and/or biliary duct) cancer, primary or secondary central nervous system tumor, primary or secondary brain tumor, Hodgkin's disease, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphoma lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, multiple myeloma, oral cancer, non-small-cell lung cancer, prostate cancer, small-cell lung cancer, cancer of the kidney and/or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system, primary central nervous system lymphoma, non-Hodgkin's lymphoma, spinal axis tumors, brain stem cancer of the spleen, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma and combinations thereof.

22. The use of Claim 21, wherein the medicament comprises the compound of claim 1.
23. The use of Claim 21, wherein the medicament comprises the compound of claim 4.
24. The use of Claim 21, wherein the medicament comprises the compound of claim 7.
25. The use of Claim 24, wherein the solvate is selected from the group consisting of ethanol/ethyl acetate mixture, 1-propanol, 2-propanol, methanol, benzene, toluene, dioxane/hexanes mixture, methyl acetate/hexanes mixture, chloroform, ethyl acetate, isopropyl acetate, methyl acetate, pyridine, anisole and trifluorotoluene solvates.
26. The use of Claim 21, wherein the solution is administered by an oral, parenteral, sublingual, buccal, intranasal, pulmonary, topical, transdermal, intradermal, ocular, otic, rectal, vaginal, intragastric, intracranial, intrasynovial or intra-articular route.
27. The use of Claim 21, wherein the neoplastic disease is a lymphoid malignancy.

28. The use of Claim 27, wherein the lymphoid malignancy is non-Hodgkin's lymphoma.
29. The use of Claim 21, wherein the medicament is administered orally in a dose of about 50 to about 1000 mg ABT-263 per day at an average treatment interval of about 3 hours to about 7 days.
30. The use of Claim 21, wherein the medicament is administered orally once daily in a dose of about 200 to about 400 mg ABT-263 free base equivalent per day.
31. A method for the treatment of a neoplastic disease selected from the group consisting of cancer, mesothelioma, bladder cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, bone cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal and/or duodenal) cancer, chronic lymphocytic leukemia, acute lymphocytic leukemia, esophageal cancer, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, hepatocellular (hepatic and/or biliary duct cancer, primary or secondary central nervous system tumor, primary or secondary brain tumor, Hodgkin's disease, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphoma, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, multiple myeloma, oral cancer, non-small-cell lung cancer, prostate cancer, small-cell lung cancer, cancer of the kidney and/or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system, primary central nervous

system lymphoma, non-Hodgkin's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, cancer of the spleen, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma and combinations thereof, the method comprising administering to a subject in need thereof a therapeutically effective amount of a medicament comprising a compound according to any one of claims 1, 4 and 7 or of a pharmaceutical composition of claim 9.

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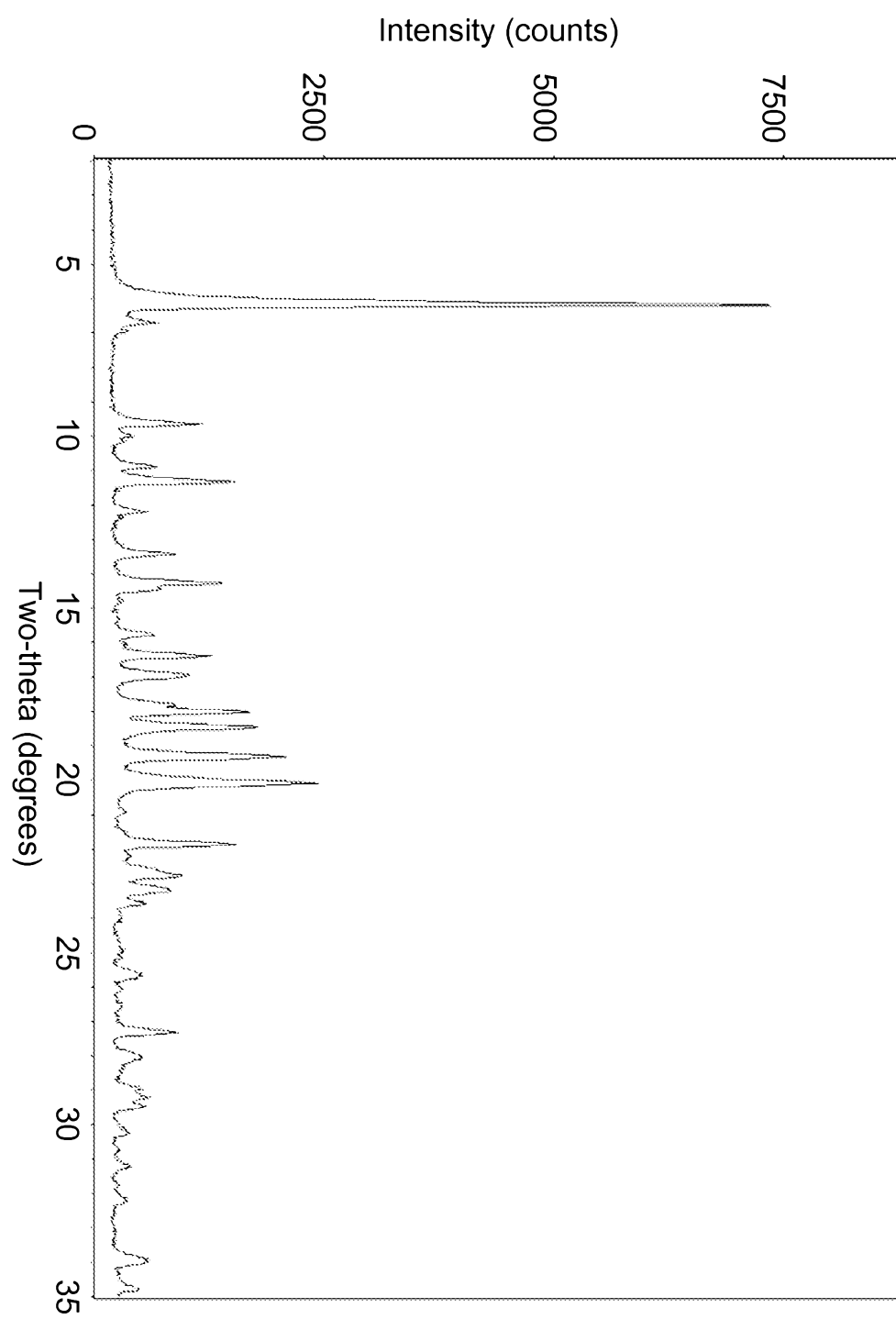


Fig. 1

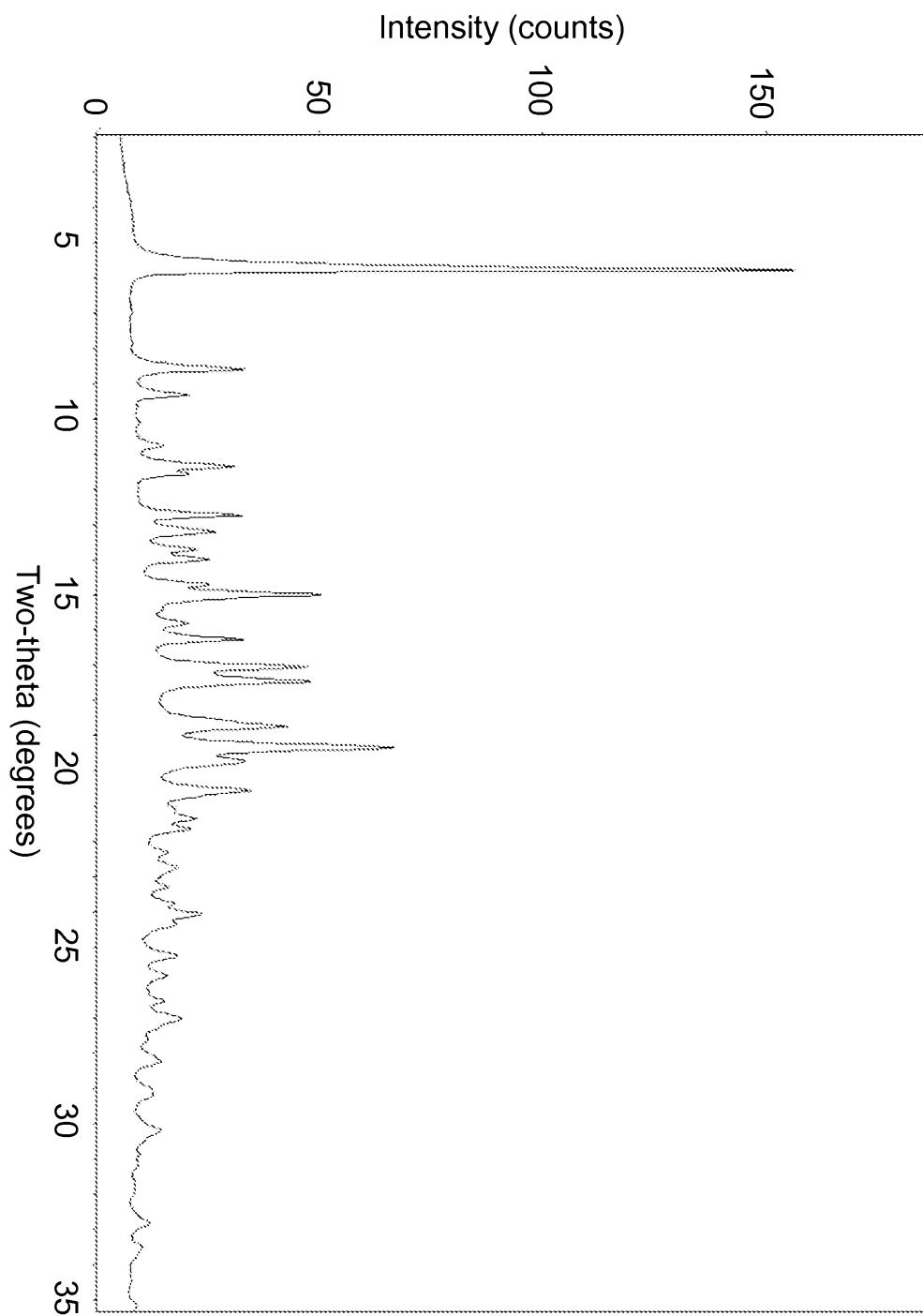


Fig. 2